การศึกษาอาการกล้ามเนื้ออ่อนแรงที่เกิดร่วมกับการระงับปวดด้วยวิธีหยดยาซาทางช่องเอปิดูราลอย่างต่อเนื่อง เปรียบเทียบระหว่าง 0.1 เปอร์เซ็นต์โรปิวาเคนผสมกับเฟนตานิลและ 0.2 เปอร์เซนต์โรปิวาเคนอย่างเดียวในผู้ป่วยหลังผ่าตัดมดลูกทางหน้าท้อง

นางวิมลรัตน์ กฤษณะประกรกิจ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาการพัฒนาสุขภาพ หลักสูตรการพัฒนาสุขภาพ
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2545
ISBN 974-17-0995-1

MOTOR BLOCKADE ASSOCIATED WITH POSTOPERATIVE ANALGESIA: A COMPARISON BETWEEN 0.1% ROPIVACAINE PLUS FENTANYL AND 0.2% ROPIVACAINE ALONE FOR CONTINUOUS EPIDURAL INFUSION AFTER ABDOMINAL HYSTERECTOMY

Mrs. Wimonrat Krisanaprakornkit

A thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Health Development
Health Development Program
Faculty of Medicine
Chulalongkorn University
Academic Year 2002

ISBN 974-17-0995-1

Thesis Title	: Motor Blockade Associated with Postoperative Analgesia: A Comparison between 0.1% Ropivacaine Plus Fentanyl and 0.2% Ropivacaine Alone for Continuous Epidural Infusion after Abdominal Hysterectomy
By	: Wimonrat Krisanaprakornkit
Field of Study	: Health Development
Thesis Advisor	: Associate Professor Somjai Wangsuphachart, M.D., M.Sc.
Thesis Co-advisor	: Professor Jariya Lertakyamanee, M.D., M.P.H.
Thesis Co-advisor	: Associate Professor Bandit Thinkhamrop, Ph.D.

Accepted by the Faculty of Medicine, Chulalongkorn University in Partial Fulfillment of the Requirement for the Master's Degree

…… Dean of Faculty of Medicine

(Professor Pirom Kamol-ratanakul, M.D., M.Sc.)

THESIS COMMITTEE

…….. Chairman

(Assistant Professor Montchai Chalaprawat, M.D., M.Sc.)

…….. Thesis Advisor

(Associate Professor Somjai Wangsuphachart, M.D., M.Sc.)

…….. Thesis Co-advisor

(Professor Jariya Lertakyamanee, M.D., M.P.H.)

…….. Thesis Co-advisor

(Associate Professor Bandit Thinkhamrop, Ph.D.)

วิมลรัตน์ กฤษณะประกรกิจ : การศึกษาอาการกล้ามเนื้ออ่อนแรงที่เกิดร่วมกับการระงับปวดด้วยวิธีหยดยาชาทางช่องเอปิดูราลอย่างต่อเนื่อง เปรียบเทียบระหว่าง 0.1 เปอร์เซนต์โรปิวาเคนผสมกับเฟนตานิลและ 0.2 เปอร์เซนต์โรปิวาเคนอย่างเดียว ในผู้ป่วยหลังผ่าตัดมดลูกทางหน้าท้อง (Motor Blockade Associated with Postoperative Analgesia: A Comparison between 0.1% Ropivacaine Plus Fentanyl and 0.2% Ropivacaine Alone for Continuous Epidural Infusion after Abdominal Hysterectomy) อ.ที่ปรึกษา : รศ.พญ.สมใจ หวังศุภชาติ M.D., M.Sc. อ.ที่ปรึกษาร่วม : ศ.พญ.จริยา เลิศอรรฆยมณี M.D., M.P.H. รศ.ดร.บัณฑิต ถิ่นคำรพ Ph.D. ; 61 หน้า ISBN 974-17-0995-1

วัตถุประสงค์: ศึกษาอัตราการเกิดกล้ามเนื้ออ่อนแรงที่เกิดร่วมกับการระงับปวดหลังผ่าตัดมดลูกทางหน้าท้องด้วยวิธีหยดยาชาทางช่องเอปิดูราลอย่างต่อเนื่อง เปรียบเทียบระหว่างการใช้ 0.1 เปอร์เซนต์โรปิวาเคนผสมกับเฟนตานิลและ 0.2 เปอร์เซนต์โรปิวาเคนอย่างเดียว ตลอดจนประสิทธิภาพในการระงับปวดด้านอื่นๆ เช่น ระดับความปวด การใช้ยาระงับปวดเสริม ภาวะแทรกซ้อน และความพึงพอใจของผู้ป่วย

รูปแบบการวิจัย: การวิจัยเชิงทดลอง แบบสุ่มและมีกลุ่มควบคุม

สถานที่ทำวิจัย: โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

ระเบียบวิธีวิจัย: ผู้ป่วยที่มารับการผ่าตัดมดลูกทางหน้าท้องและเข้าเกณฑ์การคัดเลือก 54 รายได้รับการทำ continuous epidural block ที่ระดับ L 1-2 หรือ L 2-3 ก่อนวางยาสลบ เมื่อเสร็จผ่าตัดได้แบ่งผู้ป่วยเป็น 2 กลุ่มโดยวิธีสุ่ม กลุ่มควบคุม (R) ได้รับ 0.2%โรปิวาเคนอย่างเดียวขณะที่กลุ่มทดลอง (RF) ได้รับ0.1%โรปิวาเคนผสมกับเฟนตานิล 2 มคก/มล. หยดในอัตรา 8 มล/ชม.เป็นเวลา 21 ชม. ทุกรายได้รับการติดตั้งเครื่อง PCA (Intravenous Patient-Controlled Analgesia) เพื่อให้ morphine เป็นยาระงับปวดเสริมทางหลอดเลือดดำเมื่อต้องการ ประเมินอาการอ่อนแรงของกล้ามเนื้อโดยใช้ modified Bromage scale ประเมินระดับความปวดด้วย VAS (Visual Analogue Scale) ปริมาณการใช้ morphine เป็นยาระงับปวดเสริมและระดับการชา ตลอดจนภาวะแทรกซ้อนที่เวลา 4, 8 แ ละ 21 ชม. และประเมินความพึงพอใจต่อการระงับปวดที่เวลา 21 ชม.

ผลการศึกษา: ข้อมูลพื้นฐานของผู้ป่วยทั้ง 2 กลุ่ม มีความคล้ายคลึงกันในด้านอายุ น้ำหนัก ส่วนสูง และระดับที่ใส่สายเข้าช่องเอปิดูราล ยกเว้นในเรื่องของ ASA status ระยะเวลาในการผ่าตัดและการได้รับยาชาเพิ่มระหว่างผ่าตัดที่กลุ่ม RF มีมากกว่ากลุ่ม R อัตราการเกิดกล้ามเนื้ออ่อนแรงที่เวลา 4 ชั่วโมงพบว่าข้อมูลที่ได้ไม่เพียงพอที่จะสรุปว่าทั้งสองกลุ่มแตกต่างกัน แต่ที่เวลา 8 ชั่วโมง ขีดจำกัดล่างของช่วงเชื่อมั่นที่ 95% ของผลต่างอัตราการเกิดอาการกล้ามเนื้ออ่อนแรงในผู้ป่วยกลุ่ม RF เมื่อเทียบกับกลุ่ม R (-3.7%) บ่งชี้ว่ากลุ่ม RF มิได้ด้อยไปกว่ากลุ่ม R ส่วนที่เวลา 21 ชั่วโมงกลุ่ม RF มีกล้ามเนื้ออ่อนแรงน้อยกว่ากลุ่ม R (ขีดจำกัดล่างของช่วงเชื่อมั่นที่ 95 % : 1.8%) ทั้งนี้การวิเคราะห์ได้คำนึงถึงความแตกต่างในเรื่องของข้อมูลพื้นฐานดังกล่าวแล้ว ส่วนประสิทธิภาพในการระงับปวดทั้งสองกลุ่มไม่แตกต่างกันทั้งในด้านของ VAS และการใช้ morphine ในแต่ละช่วงเวลา ยกเว้นปริมาณ morphine รวมที่พบว่ากลุ่ม RF ใช้ morphine ค่อนข้างน้อยกว่ากลุ่ม R (12 มก VS 20 มก, p=0.049) ระดับการชา ภาวะแทรกซ้อนตลอดจนความพึงพอใจของทั้งสองกลุ่มไม่แตกต่างกัน

สรุป: อาการกล้ามเนื้ออ่อนแรงที่พบร่วมกับการระงับปวดด้วยวิธีหยดยาชาอย่างต่อเนื่องทางช่องเอปิดูราลด้วย 0.1% โรปิวาเคนผสมกับเฟนตานิล ที่เวลา 8 ชั่วโมงไม่ด้อยไปกว่าการใช้ 0.2% โรปิวาเคนอย่างเดียว หลังจากนั้นอาการดังกล่าวพบน้อยกว่า ประสิทธิภาพในการระงับปวด ตลอดจนภาวะแทรกซ้อนและความพึงพอใจของผู้ป่วยไม่แตกต่างกัน แต่มีแนวโน้มที่จะต้องการยาแก้ปวดเสริมน้อยกว่า การใช้ 0.1% โรปิวาเคนผสมกับเฟนตานิลในการระงับปวดแทนการใช้ 0.2 % โรปิวาเคนอย่างเดียว จะมีโอกาสเกิดพิษจากยาชาน้อยกว่า หากสายที่ใส่เข้าไปในช่องเอปิดูราลเคลื่อนเข้าไปในหลอดเลือด

ภาควิชา	การพัฒนาสุขภาพ	ลายมือชื่อนิสิต.....
สาขาวิชา	การพัฒนาสุขภาพ	ลายมือชื่ออาจารย์ที่ปรึกษา.....
ปีการศึกษา	2545	ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....
		ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

##4375430030 MAJOR HEALTH DEVELOPMENT
KEYWORD: MOTOR BLOCKADE/ ROPIVACAINE/ CONTINUOUS INFUSION/ ABDOMINAL HYSTERECTOMY/ FENTANYL
WIMONRAT KRISANAPRAKORNKIT: MOTOR BLOCKADE ASSOCIATED WITH POSTOPERATIVE ANALGESIA: A COMPARISON BETWEEN 0.1% ROPIVACAINE PLUS FENTANYL AND 0.2% ROPIVACAINE ALONE FOR CONTINUOUS EPIDURAL INFUSION AFTER ABDOMINAL HYSTERECTOMY. THESIS ADVISOR: ASSC.PROF.DR.SOMJAI WANGSUPHACHART, M.D., M.Sc., THESIS CO-ADVISOR: PROF.DR.JARIYA LERTAKYAMANEE M.D., M.P.H., ASSC.PROF.BANDIT THINKHAMROP, Ph.D. ; 61 pp. ISBN 974-17-0995-1

Objectives: To compare the motor blockade, analgesia, adverse effects and patient satisfaction between 0.1% ropivacaine plus fentanyl and 0.2% ropivacaine alone for continuous epidural infusion after abdominal hysterectomy.

Study design: Randomized controlled trial

Setting: Srinagarind Hospital, Faculty of Medicine, Khon Kaen University

Research Methodology: Fifty-four women undergoing elective abdominal hysterectomy received continuous epidural block at L1-2 or L 2-3 before the start of general anesthesia. After surgery the patients were randomly allocated into two groups; group R received 0.2% ropivacaine alone, whereas group RF received 0.1% ropivacaine plus fentanyl 2 mcg/ml for continuous epidural infusion at 8 ml/hr. All received patient-controlled analgesia (PCA) using intravenous morphine for additional analgesic as required. Outcome measures included motor blockade (modified Bromage scale), pain intensity (VAS), morphine consumption, level of sensory blockade as well as any adverse effects. These measures were done at 4, 8 and 21 hour of infusion. At 21 hour the patients were asked about their satisfaction on pain mangement.

Results: The two groups were similar in term of age, body weight, height and site of catheter insertion. However group RF consisted of slightly more patients in ASA status 2, got longer duration of surgery and got additional dose of ropivaciane during surgery. Regarding the rate of motor blockade (adjusted for the difference in baseline characteristics), the lower boundary of 95% CI of the difference at 4 hour (-12.6%) was beyond the magnitude that we can conclude that the two groups were comparable. In contrary, the lower boundary of 95% CI of difference at 8 hours (-3.7%) indicated that group RF was not inferior as compared to group R. At 21 hours group RF had less motor blockade than group R (the lower boundary of 95% CI of difference: 1.8%). There were no differences in VAS, level of sensory blockade, adverse effects and patient satisfaction between the two groups. Morphine consumption at each time of measurement were comparable but the total amount in group RF was slightly less than group R (12 mg VS 20 mg, p=0.049).

Conclusion: At 8 hours, the rate of motor blockade produced by 0.1% ropivacaine plus fentanyl was not inferior as compared to that produced by 0.2% ropivacaine alone. After that, it produced less motor blockade. Though no difference in pain intensity was detected, morphine consumption was slightly lower. Since lower concentration of local anesthetic confers lower risk of toxicity if intravascular migration of epidural catheter occurred, 0.1% ropivacaine plus fentanyl could be a better alternative in postoperative epidural analgesia.

Department of Health Development	Student's signature……..
Field of Study Health Development	Advisor's signature……
Academic year 2002	Co-advisor's signature……
	Co-advisor's signature……

ACKNOWLEDGEMENTS

I would like to thank the Thai CERTC Consortium and the Graduate School of Chulalongkorn University for giving me the opportunity to participate in this prestigious program and also the Faculty of Medicine, Khon Kaen University for giving me the fellowship. My special thanks to Prof. Dr. Pisake lumbiganon and Assist. Prof. Dr.Sanguansak Thanaviratananich for introducing me to this program.

My gratitude is extended to Assist. Prof. Dr. Montchai Chalaprawat, the former Director of Chulalongkorn Clinical Epidemiology Unit, for his invaluable advice, comments and suggestions. Special thanks to Assoc. Prof. Dr. Somjai Wangsuphachart, my advisor, for her invaluable advice, comments and suggestion.

I wish to express my deep gratitude to Prof. Dr. Jariya Lertakyamanee, my co-advisor and former anesthesiology teacher and Assoc. Prof. Bandit Thinkhamrop, my co-advisor, for their invaluable advice, comments, suggestions and support during the study period.

I would like to acknowledge the following persons; Mr. Chedsada Noppawinyoowong and Ms. Janya Srisangchun, the pharmacists at Srinagarind Hospital, for their help in preparing the drugs used in this study. My special thanks is extended to Assoc. Prof. Dr. Somboon Thienthong, Assist. Prof. Dr. Panarat Ratanasuwan, Mrs. Kanchana Uppan, Mrs. Sasivimon Pongjanyakul and Mrs. Kaewjai Cumsook, for their invaluable assistance in data collection and processing. My grateful thanks to Assoc. Prof. Thepakorn Sathitkarnmanee, Head of the department of Anesthesiology at the Faculty of Medicine, Khon Kaen University, for his support during the study period.

My deepest appreciation to my family for giving me the opportunity to study this program and providing support, encouragement and motivation during my work in this program.

Finally, I would like to thank all patients and all personnel in Srinagarind Hospital involved with this research for their co-operation. Also I wish to thank all personnel in the clinical epidemiology unit both in Khon Kaen and Chulalongkorn University for their kindness and helpfulness in processing this thesis.

CONTENTS

CONTENTS (Continued)

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1

BACKGROUND AND RATIONALE

Postoperative pain, an unpleasant and emotional experience, is a common sequel of surgery. The consequences of pain are suffering and adverse physiologic sequel to various organ systems (1). Optimum postoperative pain management not only results in comfort and well being of the patient, but also beneficially influences the outcome of surgery by reducing complications such as pulmonary infection and chronic pain (2).

After major surgery, epidural analgesia has been shown to attenuate stress response, reduce complications, allow early ambulation and improves rehabilitation by decreasing dynamic pain, i.e. pain with moving, coughing and breathing deeply (3-6). Epidural analgesia can be given by continuous infusion or by patient-controlled epidural analgesia (PCEA). Bupivacaine, in low concentrations alone or in combination with opioid, is commonly used for these purposes (7).

Recently, a new local anesthetic, ropivacaine, was introduced which has less cardiotoxicity than bupivacaine when given in equimolar concentrations (8). However, direct comparisons of epidural anesthesia, using the same concentration, showed that ropivacaine was less potent than bupivacaine (9-12) though the difference was less marked on sensory blockade than motor blockade. At lower doses, ropivacaine caused similar sensory but less motor blockade when compared with bupivacaine (13, 14). This would be an advantage in indications such as labor and postoperative analgesia when motor blockade is undesirable.

For postoperative continuous infusion, 0.2 % ropivacaine is recommended since it provides the best balance of analgesia and minimal motor blockade (8, 15). After lower abdominal and pelvic surgery, however, continuous infusion of 0.2% ropivacaine with an upper lumbar catheter produced motor blockade in a number of patients (16-18). Since an epidural catheter should be inserted at the spinal level appropriate to the dermatome covering the planned surgical incision (19), continuous epidural analgesia with low thoracic or upper lumbar catheter is suitable for lower abdominal and gynecologic surgery. Although

the placement of catheter at thoracic vertebral level does not confer higher risk than the placement at lumbar level (3), the latter is preferable because of an easier anatomical approach (19). Since lumbar catheter has demonstrated higher motor blockade effects (odds ratio 2.1, 95% CI: 1.5-3.2) (20), an appropriate anesthetic drug should be selected in order to provide effective analgesia but minimal motor blockade.

This study aimed to compare the motor blockade associated with continuous epidural infusion using lumbar catheter and also the analgesia yielded by 0.2% ropivacaine, which is recommended, with the combination of 0.1% ropivacaine and a commonly used opioids, fentanyl 2 mcg/ml for postoperative pain control after abdominal hysterectomy.

CHAPTER 2

REVIEW OF RELATED LITERATURE

2.1 Postopertive Pain after Abdominal Hysterectomy

Abdominal hysterectomy is a common gynecologic surgery. Khun found that 94% of women undergoing abdominal hysterectomy reported moderate to severe pain (21). The mean VAS pain score during the first 24 hours was 60.5. Though there was a gradual reduction of pain during the following days, moderate to severe postoperative pain prevents early ambulation, and may initiate the other postoperative complications such as pulmonary complication, gastrointestinal ileus and prolonged hospital stayed.

2.2 Epidural Analgesia for Postoperative Pain Control

According to the pain pathway, pain arises from direct activation or sensitization of primary afferent neurons, which have cell bodies located in the dorsal root ganglion (22). Nociceptive impulse is transmitted through small myelinated Aδ and unmyelinated C fibers and synapse with the second order neurons in three of the six (laminae I, II and V) anatomically distinct layers of the dorsal horn. From the initial synapse, there are multiple neuronal synaptic connections among all the dorsal horn before transmission to the central ascending pathways such as spinothalamic tract and spinoreticulothalamic tract, which then synapse in the thalamus. Nociceptive transmission then reaches the cortex via thalamocortical projection. Mitigation of nociception at the peripheral and central levels may be accomplished through a variety of techniques including regional anesthesia and analgesia.

Epidural analgesia is an effective treatment for controlling pain after major surgery. Combining two or more drugs with different mechanisms of analgesia and different side-effect profiles can optimize the efficacy and safety of epidural analgesia (2). The drugs commonly used for epidural analgesia were local anesthetics (bupivacaine 1 mg/ml), and opioid (fentanyl 2 mcg/ml) and an adrenergic agonist (epinephrine 2 mcg/ml). Fentanyl and epinephrine act on pre and postsynaptic opioid receptors and α2 receptors, respectively, to increase inhibition of pain impulse

transmission from the primary afferent nociceptive neurons to the interneurons and transmission neurons in the dorsal horn of the spinal cord. Subanesthetic dose of bupivacaine inhibits excitatory synaptic mechanisms in the same area of spinal cord.

A Cochrane review showed that the administration of epidural local anesthetics to patients undergoing laparotomy reduces gastrointestinal paralysis compared with systemic or epidural opioids, with comparable postoperative pain relief (23). Addition of opioid to epidural local anaesthetic may provide superior postoperative analgesia compared with epidural local anesthetics alone. For pulmonary complication, meta-analysis by Ballantyne showed that epidural local anesthetics, with or without opioids, decreased the risk of pulmonary complications such as atelectasis and pneumonia by 50-70% compared with systemic opioid alone (5).

In epidural analgesia, the drugs used can be given either by bolus injection or continuous infusion (7). Intermittent injection provides analgesia for a prolonged period but needs to be re-injected at appropriate time, usually by acute pain service team. Continuous infusion, by infusion pump, provides stable level of analgesia. The use of special and quite expensive type of infusion pump permits the patient to get small additional doses of drugs whenever required, known as patient-controlled epidural analgesia (PCEA).

2.3 Ropivacaine for Epidural Anesthesia and Analgesia

Ropivacaine is an aminoamide local anesthetics (24). It is the monohydrate of the hydrochloride salt of 1-propyl-2', 6'- pipercoloxylidide and is prepared as the isomerically pure in the S-enantiomer form. Ropivacaine has a pK_a similar to that of bupivacaine (~ 8.1), which is a homologue racemic praparation, but, because of its different structure, is less lipid soluble (octanol/buffer partition coefficient 115 VS 346). Plasma protein binding is marginally less than that of bupivacaine. The physicochemical properties suggest that its rate of onset (related to pK_a) should be similar to that of bupivacaine, and that its absolute potency (lipid solubility) and duration of effect (protein binding) should be slightly less.

Ropivacaine was first registered for use in 1996. It differs in terms of toxicity from bupivacaine. Animal and *in vitro* studies demonstrated less cardiotoxic effect from

ropivacaine than bupivacaine (25, 26). In volunteers, ropivacaine produced CNS toxicity at a much higher plasma level than bupivacaine (27). Ropivacaine was more selective for A δ and C fibers (responsible for pain) than A β fibers (responsible for motor function) (28). The lower cardiotoxicity and the greater sensory-motor separation properties of epidural ropivacaine make it an attractive agent for labor and postoperative pain management.

For postoperative epidural analgesia, continuous infusion of 0.2% ropivacaine at 6-14 ml/h is recommended for lumbar catheter (24). After abdominal and pelvic surgery, continuous epidural analgesia with catheter inserted at T_{12}-L_4 has been shown to provide effective pain control with variable levels of motor blockade. Scott *et al.* reported that at the same infusion rate (10 ml/h) with catheter insertion between T_{12}-L_2, the rate of motor blockade assessed after 8 hours of infusion by was 20%(15), while Jayr *et al.* reported 40%(16). By contrast, Chinachoti *et al*. used a rate of 8 ml/h with the same insertion level but found that 55% of the patients suffered from motor blockade at the same period (17). Moreover, Wong *et al*. found motor blockade in 45% of the patients with the average rate at 6.5 ml/h in patient- controlled epidural analgesia (PCEA) (29). Although there was a dose-related increase in the amount of motor blockade, Turner *et al*. showed that the rate of motor blockade did not vary between infusion rates of 6 and 8 ml/h (30). This result was in contrast with that reported by Etches *et al.*, who found 20% and 45% motor blockade at the infusion rates of 6 and 8 ml/h, respectively (18). But the difference should be interpreted with caution since the level of catheter insertion in the study of Etches ranged from T_9 to L_4. With a thoracic catheter, the rate of motor blockade is low as Jorgensen *et al*. reported that only 7% of patients experienced motor blockade with continuous infusion at 8 ml/h (14).

Since the level of catheter insertion is an important factor related to the incidence of motor blockade (20), therefore the more favorable lumbar spinal level should be used with the appropriate anesthetic agent for postoperative epidural analgesia.

The efficacy of continuous lumbar epidural infusion with less than 0.2% ropivacaine has been evaluated. In volunteers, 0.1% ropivacaine produced limited analgesia but less motor blockade, a higher success rate than 0.2 % in the attempt to

mobilize (31) and in better postural control (32). In dose- finding studies for postoperative pain control, Badner *et al*.(33) and Scott *et al*.(15) found similar analgesia in terms of Visual Analogue Scale (VAS) pain score and Intravenous Patient-Controlled Analgesia (IVPCA) morphine consumption between 0.1% and 0.2% ropivacaine after major orthopaedic and lower abdominal surgery. There was also no significant difference in motor blockade although no patient in the 0.1% ropivacaine group showed motor blockade compared with 20% of patients in the 0.2% ropivacaine group. In both studies, they did not provide the detail about calculation of the sample size to pre-determine the statistical power and included only 10 to 12 subjects per group. Notwithstanding, although not statistically significant, there was a trend that patients receiving 0.1% ropivacaine required more additional analgesic than those receiving 0.2% after lower abdominal surgery. These might indicate lower efficacy of 0.1% ropivacaine in postoperative analgesia after lower abdominal surgery. In contrast with orthopaedic surgery, Kampe *et al*. demonstrated effective pain control after total hip replacement with 0.1% ropivacaine and found motor blockade in less than 7% of patients at 8 hours (34).

In Srinagarind Hospital, Khon Kaen University, abdominal hysterectomy is the most common operation in gynecologic surgical patients. Moderate to severe postoperative pain is not an uncommon experience in women undergoing this surgery (21, 35). Lumbar epidural analgesia by ropivacaine continuous infusion is an alternative to improve the quality of postoperaive pain management in these patients.

The undesirable motor blockade associated with lumbar catheter can be reduced by various techniques such as decreasing the infusion rate (30), decreasing concentration of anesthetics (31, 33) and using in combination with epidural opioid (36-38). Among these techniques, the combination of a low concentration of local anesthetics with opioid is the most effective since excellent analgesia will occur by synergistic antinociceptive interaction(39). Moreover, when combined, the dose of local anesthetic can be reduced. Therefore, motor blockade is minimized. With appropriate concentration and patient observation, epidural analgesia with a combination of local anesthetic and opioid can be managed in a general surgical ward with minimal complication (40).

Ropivacaine 0.1% plus 2 mcg /ml fentanyl has been shown to provide satisfactory analgesia with minimal motor blockade using patient-controlled epidural analgesia (PCEA) with lumbar catheter after lower abdominal surgery (41) and caesarean section (37). For continuous infusion, this combination has not been evaluated for postoperative pain control.

CHAPTER 3

RESEARCH DESIGN AND RESEARCH METHODOLOGY

3.1 Research questions

3.2.1 Primary research question

Does continuous epidural infusion of 0.1% ropivacaine plus fentanyl at 8 ml/h after abdominal hysterectomy result in different motor blockade from infusion of 0.2% ropivacaine alone?

3.2.2 Secondary research question

Are there any differences between 0.1% ropivacaine plus fentanyl and 0.2% ropivacaine alone in the pain intensity, the need for additional analgesics, adverse effects and patient satisfaction?

3.2 Research objectives

The purpose of this study was to compare motor blockade, efficacy in pain relief, adverse effects and patient satisfaction between 0.1% ropivacaine plus fentanyl and 0.2% ropivacaine alone for continuous epidural infusion after abdominal hysterectomy.

3.3 Hypotheses

3.3.1 Research hypothesis

The proportion of post abdominal hysterectomy patients who suffer from motor blockade because of continuous epidural infusion of 0.1% ropivacaine plus fentanyl is less than those who received the infusion of 0.2% ropivacaine alone.

3.3.2 Statistical hypothesis

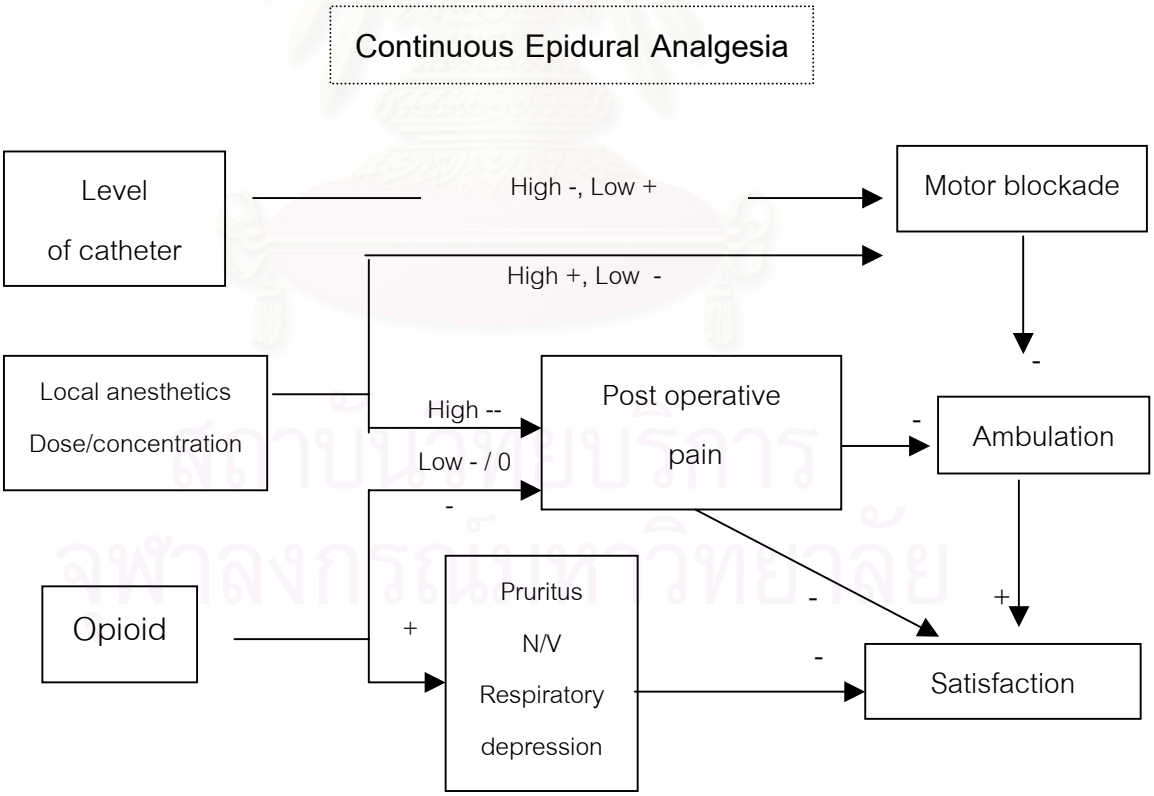
Null Hypothesis: There is no difference in the proportion of patients suffering from motor blockade whether 0.1% ropivacaine plus fentanyl or 0.2% ropivacaine alone are used.

Alternative hypothesis: Based on the use of 0.1% ropivacaine plus fentanyl and 0.2% ropivacaine alone, there is a difference in the proportion of patients suffering from motor blockade.

3.4 Conceptual framework

In continuous epidural analgesia, level of catheter insertion and the amount of local anesthetic drug used influence the motor blockade. The higher the level of catheter insertion as well as the lower amount of local anesthetic used, the less motor blockade occurs which promote early ambulation. However, analgesia that results from the lower amount of local anesthetic might not be adequate. Adding opioid into the solution can improve analgesia but can cause some adverse effects which influence patient satisfaction.

Figure 1 Conceptual framework



3.5 Key Words

Motor blockade

Ropivacaine

Continuous infusion

Abdominal hysterectomy

Fentanyl

3.6 Operational Definition

3.6.1 Abdominal hysterectomy: Total abdominal hysterectomy ± salpingo-oophorectomy

3.6.2 Motor blockade: Modified Bromage score more than 0

3.6.3 Hypotension: Systolic blood pressure lower than 30% of control or lower than 80 mmHg.

3.6.4 Respiratory depression: Respiratory rate lower than 10 /minute

3.6.5 Excessive sedation: Sedation scores more than 3

3.7 Research Design

This was a randomized, double -blind, controlled clinical trial.

3.8 Target population

Women undergoing abdominal hysterectomy

3.9 Sample population

All gynecologic surgical patients at Srinagarind Hospital who met the following inclusion criteria.

3.10. Eligibility criteria

3.10.1 Inclusion criteria

1. Patients aged 30 to 65 year old
2. Body weight 40 to 75 kg
3. ASA physical status 1 or 2 (Appendix A)

4. Understand how to rate visual analogue scale and how to use patient-controlled analgesia equipment
5. Informed consent obtained

3.10.2 Exclusion criteria

1. Contraindication to epidural anesthesia
2. Allergy to local anesthetics or opioids
3. Co-existing disease which could affect the reliability of the clinical assessment
4. Known or suspected drug abuse
5. Failure of epidural catheter insertion

3.11 Sample size

Since the primary outcome is motor blockade at 8 hours after surgery, the sample size calculation is based on the following formula (42) :

$$n / group = \frac{\{ Z_{1-\alpha/2} \sqrt{2\bar{p}(1-\bar{p})} + Z_{1-\beta} \sqrt{P_A(1-P_A) + P_B(1-P_B)} \}^2}{(P_A - P_B)^2}$$

For 2 sided α- error 5 %, $Z_{1-\alpha/2} = 1.96$ β- error 20% , $Z_{1-\beta} = 0.84$

$P_A = 0.55$ (17) $P_B = 0.15$ $\bar{p} = (P_A + P_B)/2 = 0.35$, n / group $= 20.8 \approx 21$

drop out 10% , n/ group (43) $= 21 / (1 - 0.1)^2 = 25.92 \approx 26$

Based on the rate of 55% motor blockade in the control group, a sample size of 21 per group would have 80% power to detect a difference of 40% in a two- sided test at the 0.05 level of significance. To allow for a 10% drop out rate, the sample size required should be 26 patients per group and a total number of 52.

3.12 Allocation technique

Patients were randomly allocated into two groups by permutated block randomization using a computer generated random number (44). The random number code was written on a paper and enclosed in a sealed opaque envelope to ensure concealment of the allocation. The pharmacist, not involved in evaluation of the patients, prepared the solution according to the code. The code was kept confidential until the time of data analysis.

3.13 Intervention

Pre operative period

Before surgery, eligible patients were instructed how to use patient-controlled analgesia equipment, to rate pain on the visual analogue scale and to ask for antiemetic and antipruritic drugs when needed. Routine preoperative preparation was performed. For premedication, the patients recieved diazepam 5 mg per oral 2 hours before surgery.

Anesthesia and intra operative period

In the operating room, the patients were monitored with noninvasive blood pressure monitoring, electrocardiogram and pulse oximeter (all by Omnicare; Agilent). At least 500 ml of Ringer Lactate solution was given to the patients over 15 minutes before epidural block.

Epidural anesthesia:

Under standard aseptic technique, the patient was kept in a lateral position and skin infiltration was done at L_{1-2} or L_{2-3} interspaces. With a 16 or 18-gauge Tuohy needle, the epidural space was identified by the loss of resistance technique. Then a multiorifice Portex® epidural catheter was inserted to the depth of 3 to 5 cm in the cephalad direction. A test dose of 1.5% lidocaine with adrenaline 1:200000 3 ml was given after negative aspiration for cerebrospinal fluid and/or blood. Five minutes later, 10 ml of 0.75% ropivacaine was given over 5 minute. Anesthesia was assessed with pinprick method every 5 minutes. If sensory block did not reach T_{10} within 15 minute after injection, an additional 5 ml. top-up dose was administered. If the total dose of 15 ml

could not produce anesthesia up to the T_{10} level within 30 minutes after the first injection, the patient was excluded as a failed epidural block.

General anesthesia and surgery:

After T_{10} anesthesia was achieved, standard general anesthesia with endotracheal intubation was induced (Appendix 2) and surgery was performed as usual. During surgery, fentanyl supplement up to 50 mcg was given only if there was a sign of inadequate analgesia. Fluid management was administered according to the condition of the patients in order to maintain normal vital signs. Hypotension was treated with volume replacement and ephedrine 3 to 6 mg intravenously (IV) if necessary. An additional 5 ml of 0.75% ropivacaine was given every 2.5 hours until surgery was complete. At the end of surgery, the muscle relaxant was reversed and the patients were extubated and admitted to postoperative care unit (PACU).

Postoperative period

According to the randomization sequence, the patients got epidural infusion with either 0.1% ropivacaine + 2 mcg/ml fentanyl or 0.2% ropivacaine alone at 8 ml/h (IVAC 591 volumetric infusion pump) when they arrived at the PACU. This infusion was continued for 21 hours post operation.

All patients had intravenous patient-controlled analgesia (PCA II; Baxter) with morphine 1 mg/ml connected to the IV line for 21 hours. PCA setting was 1 mg bolus dose with a 5-minute lockout period and a 20 mg limit per 4 hours. No other systemic narcotic was given. The patients stayed in PACU for at least 2 hours. Patient monitoring was done as usual except for the outcome measures.

Hypotension was treated by volume replacement or ephedrine 3 to 6 mg IV if nessessary. Naloxone 0.1 to 0.4 mg IV was given in case of respiratory depression. Pruritus was treated by 10 mg chlorpheniramine IV. Nausea and vomiting was treated with 10 mg metoclopramide as the first line drug. Ondansetron 4 mg IV was used in case of intractable nausea and vomiting.

Overall study design is shown in Appendix C.

Control to prevent co-intervention and contamination

- The patients and the attending physicians were thoroughly informed about the study protocol in order to prevent co-intervention. Only the research team managed the pain.

- The study drugs were freshly prepared and labeled with the code for each patient by a pharmacist not involved in the patient's care. Each patient received a coded drug epidurally. The epidural line was well protected from the other IV line.

- The patients could administer rescue analgesic by themselves if they experienced pain by using IVPCA. Side effects were closely monitored and readily managed as indicated. The outcome assessments which would disturb the patients were not performed between 22:00 and 6:00. The compliance of the patients would be easily and closely monitored.

3.14 Outcome variables and measurement

Primary outcome

- **Motor blockade** : Binary outcome

Muscle power was assessed with a modified Bromage score (19) (Score 0 = no motor block, 1 = inability to raise extended legs, 2 = inability to flex knees and 3 = inability to flex ankle joints). The modified Bromage score is the most commonly used score for motor blockade evaluation after spinal and epidural anesthesia. Motor blockade was defined as a modified Bromage score > 0. When there was unequal blockade in the 2 legs, the higher degree was recorded.

Secondary outcomes:

- **Pain intensity:** Continuous outcome

Pain was assessed to determine the analgesic efficacy at rest and on coughing with a 0 to 100 mm visual analogue scale (VAS) on which 0 indicated no pain and 100 the worst pain imaginable.

- **Additional analgesic requirement**: Continuous outcome

Morphine consumption in mg from intravenous PCA equipment was used to assess analgesic efficacy.

♦ **Sensory blockade:** Ordered categorical outcome

Both upper and lower level sensory block was assessed using the pinprick method. If there was unequal blockade, the lower segment was recorded.

♦ **Adverse effects**

- **Hypotension**: Binary outcome

Blood pressure was measured with sphygmomanometer as routinely used. Systolic blood pressure lower than 30% of control or lower than 80 mmHg was defined as hypotension.

- **Respiratory depression:** Binary outcome

Respiratory rate was observed. Respiratory rate < 10/minute was defined as respiratory depression.

- **Excessive sedation**: Binary outcome

Sedation was assessed using a sedation score (40) (0 = awake and fully alert, 1 = mildly drowsy, 2 = moderately drowsy, 3 = very drowsy but possible to arouse, 4 = difficult to arouse or unresponsive and S = normal sleep). Sedation score > 3 was considered excessive sedation.

- **Nausea/vomiting:** Ordered categorical outcome

Nausea/ vomiting was rated by the patients on a 5-point rating scale as 1 = no N/V, 2 = mild with no treatment required, 3 = moderate with treatment required, 4 = severe with successful treatment, 5 = severe despite treatment.

- **Pruritus:** Ordered categorical outcome

Degree of pruritus was rated by the patients on a 5-point rating scale as 1 = no pruritus, 2 = mild with no treatment required, 3 = moderate with treatment required, 4 = severe with successful treatment, 5 = severe despite treatment.

♦ **Patient satisfaction:** Ordered categorical outcome

The patients rated global assessment of satisfaction with postoperative pain management on a 4-point rating score: excellent, good, fair and poor.

Control for validity and reliability of the outcome measures.

The measurements used, such as the modified Bromage and sedation scores, are widely accepted in anesthesia practice and literature. The observers were trained

and tested for good inter rater reliability before collecting the data. Kappa coefficient was 0.9, which indicated high level of agreement between the two observers.

3.15 Data collection

Demographic and baseline data, such as age, body weight, ASA physical status, level of catheter insertion and duration of surgery, were recorded. After performing the epidural infusion, a modified Bromage score was assessed to identify any motor blockade at 4, 8 and 21 hours. For analgesic efficacy, the VAS score, level of sensory blockade and amount of morphine consumption were recorded at the same time as the motor blockade evaluation. All variables except morphine consumption were not assessed between 22:00 and 6:00 o'clock. Data about adverse effects were recorded every 4 hours for respiratory depression, hypotension and excessive sedation. Other adverse effects such as nausea/vomiting and pruritus were recorded at 4, 8 and 21 hours after infusion. At 21 hours of infusion, the patient's satisfaction was recorded.

3.16 Data processing and data analysis

After the data collection forms were filled completely, the researcher assigned the code corresponding to each group according to the randomization code. Then two independent key operators entered the data to the computer. These double data entry process then was validated against each other. Mismatch record would be corrected.

Demographic and baseline continuous variables such as age, body weight and duration of surgery were presented as means (S.D.) if they were normally distributed. If not, median (range) was used. Categorical variables, such as ASA physical status and level of catheter insertion, were presented as proportions. The aim was to discern similarities between the two groups' baseline characteristics.

To answer the research question, in which the primary outcome was binary, the proportion of patients suffering from motor blockade was estimated for each group then the difference and its 95% confidence interval were estimated. To analyze the significant difference of the proportion between the two groups, the Z- test was used.

Secondary binary outcomes, including hypotension, respiratory depression and excessive sedation, were analyzed in a similar way as for the primary outcome. Ordinal

outcomes, i.e., upper and lower level sensory blockade, were presented as median and range and tested for the difference using Mann- Whitney *U* test. Other ordinal outcomes including nausea/vomiting and pruritus were presented as percentages and tested using the χ^2- test for trend.

VAS and morphine consumption are continuous variables, and their data would be presented as means (S.D.) if they were normally distributed; if not, the median (range) would be used. To estimate the magnitude of the difference between the two groups, Generalized Estimating Equations (GEEs)(45), which account for within-subject variations from three measurements was used.

The last outcome, patient satisfaction, which is an ordinal outcome would be presented as a percentage and tested using χ^2- test for trend.

3.17 Ethical Considerations

In anesthesia practice, continuous epidural analgesia with or without opioid is well accepted as a satisfactory method for postoperative pain management. The dosage used in this study is based on evidence of effective analgesia without serious adverse effects.

Institutional Review Board of Faculty of Medicine, Khon Kaen University approved the study protocol. The patients were thoroughly explained about the details of the study, details of intervention and also the possible adverse effects. Written informed consent was obtained before enrolling any patient into the study. The patients could withdraw whenever they wished without interference with regular care or benefit.

3.18 Limitations

1. Since failure of an epidural block and catheter insertion may affect the outcome, the procedure should be performed only by experienced anesthesiologists.

2. Rating of pain intensity needs cooperation and understanding of the visual analogue scale. If patients could not understand how to rate their pain, they should not be recruited for the study.

3. This study was conducted in a university hospital where equipments and personnel are available so the results may not be generalized to the whole population undergoing abdominal hysterectomy.

4. Although motor blockade is one important factor, many other postoperative conditions of the patients such as dizziness, fear and postural hypotension also influence their abilities to ambulate early. In anesthesia practice, any patients with residual motor blockade will not be allowed to move from bed. Therefore, instead of true ambulation, the modified Bromage score of zero was used as important surrogate outcome to predict the ability of early ambulation.

3.19 Benefits of the study

If 0.1% ropivacaine plus 2 mcg/ml fentanyl causes less motor blockade than 0.2% ropivacaine alone, it should replace the 0.2% concentration in order to increase the margin of safety of ropivacaine and to reduce the pharmacy acquisition cost of this new, expensive drug.

The results of this study will serve as the basis of future research on continuous epidural analgesia using lumbar catheter.

CHAPTER 4

RESULTS

4.1 Characteristic of the study population

Fifty-four women who underwent elective total abdominal hysterectomy (TAH) at Srinagarind Hospital during the 7 month - period from June to December 2001 were recruited into the study. Twenty-seven patients were allocated to each group. Two patients withdrew before completing the follow up, one in control (R) and the other in treatment (RF) group. The patient in group R withdrew at 8 hours of infusion because of the discomfort from intense motor blockade. The patient in group RF withdrew at 17 hours of infusion due to catheter dislodgement. Therefore the outcome measured at 21 hours of infusion had been collected from 52 patients while that measured at 4 and 8 hours of infusion had been collected from 54 patients.

The baseline characteristics of the patients in both groups were comparable regarding age, body weight, height and site of catheter insertion. See table 1 for more details. However, there were more patients in group RF than in group R (8 VS 3) who were in ASA status II which were due to mild systemic disease such as diabetes or hypertension. More patients in group RF received additional dose of ropivacaine during operation than in group R (8 VS 3). The mean duration of surgery was slightly longer in group RF than in group R (118 $\pm$ 28 min VS 105 $\pm$ 27min). These factors were adjusted for the outcome interpretation. The preoperative diagnosis and the operation performed in each group were shown in table 2 and table 3 respectively.

Table 1: Demographic and baseline data of the two groups. Values are number (%) unless otherwise indicated.

Characteristics	Group R (n = 27)	Group RF (n = 27)
Age (mean ± S.D.)	45.2 ± 8.0	44.8 ± 6.8
Median (range)	44 (35-64)	44 (31-59)
Weight (mean ± S.D.)	56.6 ± 6.8	56.8 ± 9.4
Median (range)	56 (45-71)	58 (42-74)
Height (mean ± S.D.)	154.4 ± 4.8	155.9 ± 5.1
ASA status		
ASA I	24 (88.9%)	19 (70.4%)
ASA II	3 (11.1%)	8 (29.6%)
Level of epidural catheter insertion		
L_{1-2}	2 (7.4%)	1 (3.7%)
L_{2-3}	25 (92.6%)	26 (96.3%)
Duration of operation in minute (mean ± S.D.)	105.2 ± 27.1	118.1 ± 28.1
Patients who received additional dose of 0.75% ropivacaine during surgery	3 (11.1%)	8 (29.6%)

Table 2: The preoperative diagnosis in study population. Values are number of the patients.

Preoperative diagnosis	Group R (n = 27)	Group RF (n = 27)
Myoma uteri	17	23
Carcinoma in situ (CIS)	4	2
Cervical dysplasia	5	1
Ca cervix Ia	1	1

Table 3: The operation performed in each group. Values are number of patients

Operation	Group R (n = 27)	Group RF (n = 27)
TAH only	9	4
TAH and appendectomy	5	9
TAH with unilateral SO	-	1
TAH with unilateral SO and appendectomy	1	-
TAH with unilateral SO, appendectomy and lysis adhesion	-	1
TAH with bilateral SO	6	5
TAH with bilateral SO and appendectomy	6	7

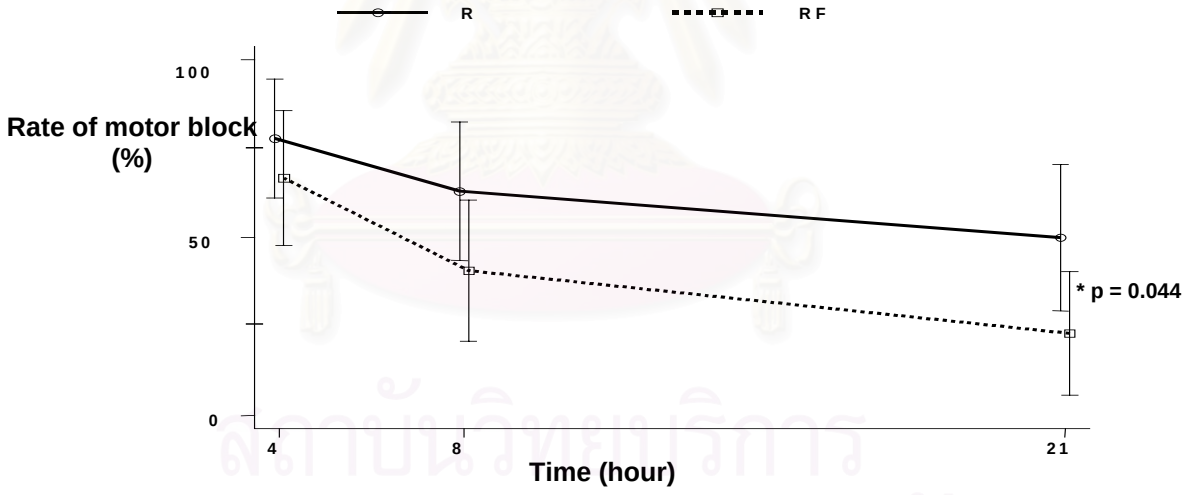
4.2 Rate of motor blockade

Motor blockade was assessed at 4 and 8 hours of infusion in 54 patients, but at 21 hours there were only 52 patients in the study. The rates of motor blockade in each assessment were shown in table 4. Overall the rates decreased over time in both groups. Group R had consistently greater rate of motor blockade than group RF at 4, 8 and 21 hours with the magnitude of difference of 11%, 22% and 27% respectively (Figure 1). However these differences were not statistically significant except at 21 hours, when we are 95% confident that such difference in the population could line between 1.8% and 52% (p-value = 0.044)

Table 4: Number of patients with motor blockade comparing between the two treatments at 4, 8 and 21 hours.

Time of measurement	Group R	Group RF	Difference (95%CI)	p value
At 4 hours (n=27/gr)	21 (77.8%)	18 (66.7%)	11.1% (-12.6%,34.8%)	0.362
At 8 hours (n=27/gr)	17 (63%)	11 (40.7%)	22.3% (-3.7%,48.2%)	0.102
At 21hours (n=26/gr)	13 (50%)	6 (23.1%)	26.9% (1.8%,52%)	0.044

Figure 2. Rate of motor blockade between control (R) and treatment (RF) group



* Z-test for proportion

Concerning the difference in baseline characteristics in terms of ASA status, duration of surgery and additional dose during surgery, the generalized estimating equation (GEEs) which is appropriate for analysis of longitudinal data was

used to control such factors. The crude and adjusted odds ratio of treatment on motor blockade were 0.40 (0.16-0.97) and 0.39 (0.16-0.97) respectively. This suggested that those factors played no role in the effect of the treatment on motor blockade. Therefore those patients who received 0.1% ropivacaine with fentanyl were 0.4 times more likely to get motor blockade compared to those who received 0.2% ropivacaine alone. The 95% confidence interval of odds ratio indicated the significant protective effect of lower concentration of ropivacaine in combination with opioid.

4.3 Analgesic efficacy: Pain intensity, level of sensory blockade and morphine consumption

The median visual analogue scales (VAS) both at rest (Figure 3) and on coughing (Figure 4) evaluated at 4, 8 and 21 hours were less than 30 mm in both groups. At rest, the median VAS were less than that on coughing in every patients. Since the distribution widely varied as shown in figure 3 and 4, the magnitude of difference were quantified by using the 95%confidence interval of median difference instead of the GEEs. However the results of analysis by using GEEs (data not shown) which is quite robust in normality assumption yielded the same results which indicated that there were no significant difference between the two groups. See table 5 for details.

Figure 3: Pain intensity in term of VAS at rest

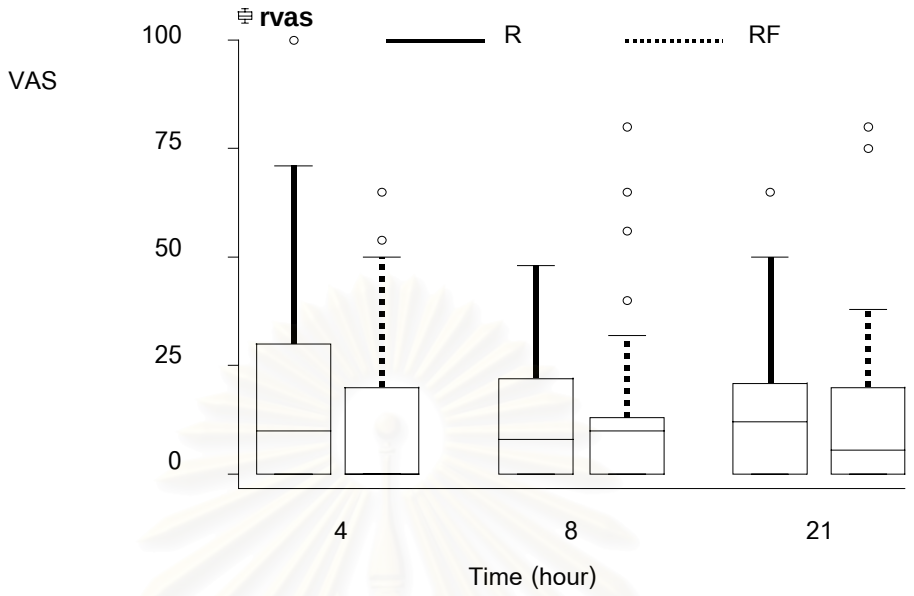


Figure 4: Pain intensity in term of VAS on coughing

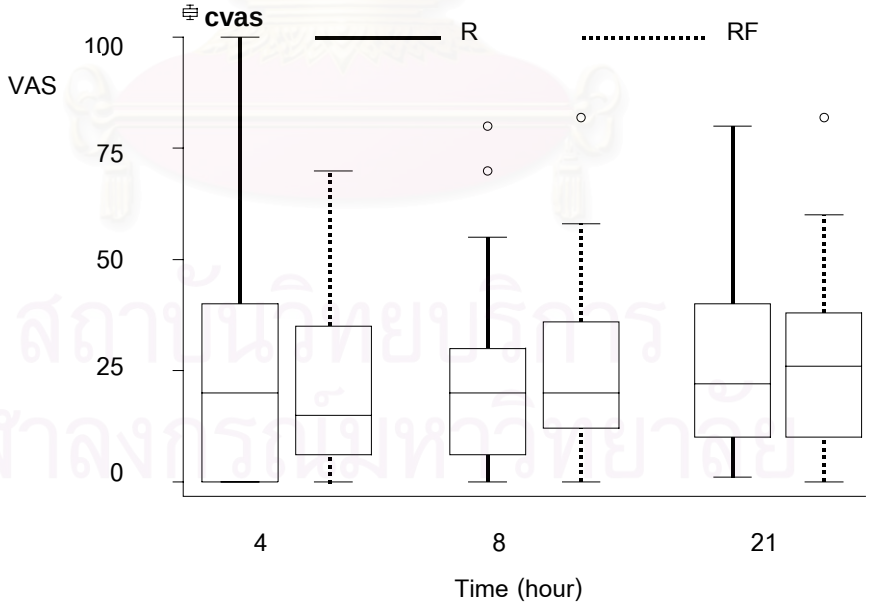


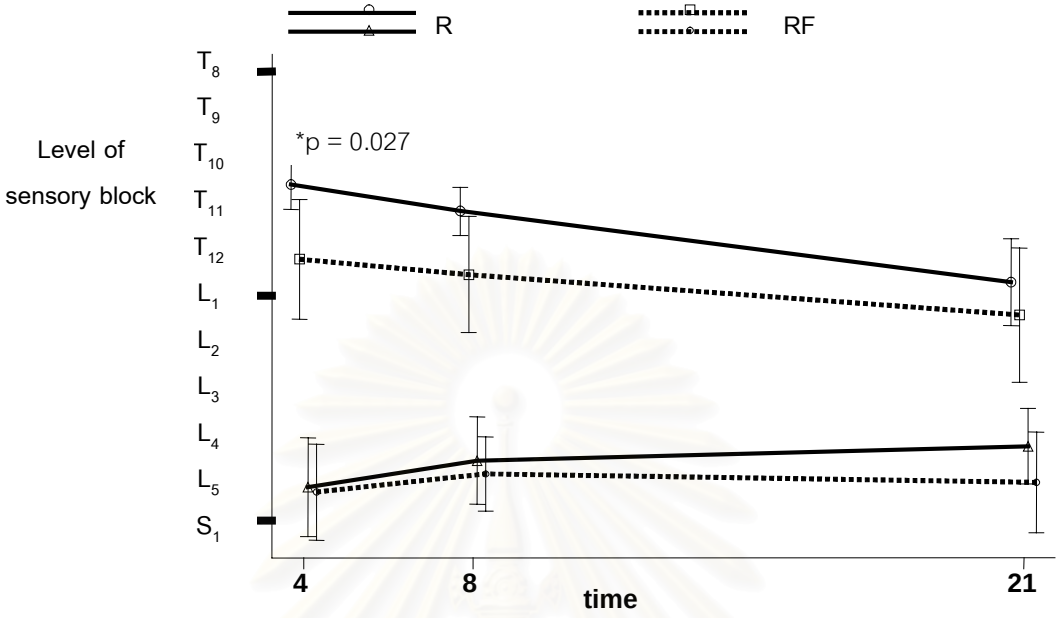
Table 5: Analgesic efficacy in term of VAS. Numbers are median (range)

Visual Analogue Scale	Group R	Group RF	Difference (95%CI)	p value*
- At rest				
At 4 hours (n=27/gr)	10 (0–100)	0 (0–65)	10 (0,10)	0.246
At 8 hours (n=27/gr)	8 (0–48)	10 (0–80)	0 (-7,8)	0.851
At 21 hours (n=26/gr)	12 (0–65)	5.5 (0–80)	2 (-2,10)	0.312
- On coughing				
At 4 hours (n=27/gr)	20 (0–100)	15 (0–70)	0 (-10,14)	0.862
At 8 hours (n=27/gr)	20 (0–80)	20 (0–82)	-2 (-12,8)	0.658
At 21 hours (n=26/gr)	22 (1-80)	26 (0–82)	0 (-10,10)	0.978

* Mann-Whitney *U* test

The upper and lower levels of sensory blockade assessed by pinprick sensation were shown in figure 5. The median level of sensory block covered the area of incision in both groups. Group RF had lower but not significantly difference from group R at every assessment except for the upper level at 4 hours which group RF had significantly lower level than group R (p value 0.027).

Figure 5: Upper and lower level of sensory blockade between the two groups



* Mann-Whitney *U* test

The amounts of morphine consumption for rescue analgesia in the two groups were not significantly different. However there was a trend toward lower amount of morphine consumption in group RF at every time of measurement. Total morphine consumption was slightly lower in group RF than in group R. Median total morphine consumption in group RF was 12 mg compared to 20 mg in group R. The difference of median was 7mg (95%CI: 0 –14 mg, p=0.049). See table 6 for details.

Table 6 : Comparing cumulative morphine consumption between the two groups. Values are median (range)

Morphine consumption (mg)	Group R	Group RF	Difference (95%CI)	p value*
0- 4 hours (n=27/ gr)	2 (0 – 14)	2 (0 – 12)	1 (-1,3)	0.309
4- 8 hours (n=27/ gr)	3 (0 – 16)	1 (0 – 10)	1 (0,3)	0.096
8-21 hours (n=26/ gr)	11.5 (0 – 34)	7 (0 – 20)	3 (-1,9)	0.160
0-21 hours (n=26/ gr)	20 (0 – 48)	12 (1 – 33)	7(0,14)	0.049

* Mann- Whiney *U* test

Taking into account for within subject variations from three measurements, GEEs was used to estimate the magnitude of difference in morphine consumption. On average group R consumed morphine more than gr. RF about 2.38 mg (95%CI: 0.31 mg - 4.4 mg, p = 0.024). This suggested that group RF required significant less amount of morphine than group R.

4.4 Adverse effects

One patient in the control group developed hypotension (BP 84/52 mmHg.) at 12 hours of infusion (12.00 p.m.). She was a 64 year-old patient without any underlying disease. Her preoperative investigations were otherwise normal except for chest X-ray that showed mild cardiomegaly and electrocardiogram, which showed occasional premature ventricular contraction. Her blood pressure before operation was 130/90 mmHg. She responded well after 100 ml. intravenous fluid loading in ten minutes and did not need vasopressor. Neither excessive sedation nor respiratory depression was detected in both groups.

Patients in the two groups had no significant difference in symptom or degree of nausea/vomiting. One patient in the treatment group had severe nausea/vomiting with successful treatment.

Similar as nausea/vomiting, the two groups were not significantly different in symptom of severity of pruritus. Severe degree of pruritus was not reported. See table 7 for more details.

Table 7 : Comparing nausea/vomiting and pruritus between the two groups. Value are number (%)

Adverse effects	Group R (n = 26)	Group RF (n = 26)	p value*
Nausea/vomiting			
No symptom	8 (30.8%)	6 (23.1%)	0.336
Mild, no treatment required	8 (30.8%)	7 (26.9%)	
Moderate, treatment required	10 (38.5%)	12 (46.1%)	
Severe, with successful treatment	0	1 (3.8%)	
Pruritus			
No symptom	22 (84.6%)	18 (69.2%)	0.174
Mild, no treatment required	3 (11.5%)	5 (19.2%)	
Moderate, treatment required	1 (3.8%)	3 (11.5%)	

* χ^2- test for trend

4.5 Patients satisfaction

There were two patients dropped out before complete follow up. So the assessment of patient satisfaction was done in only 52 patients. Of those whom were assessed, ten patients in the treatment group reported the excellent level of satisfaction compared with 8 patients in the control group. Comparable number of the patients in both groups reported good or fair level of satisfaction. No patients reported poor satisfaction. Chi square test for trend showed no significant difference (p value = 0.50). See table 7 for detail.

Table 8: Proportion of patient's satisfaction between two groups. Values are number (%)

Level of satisfaction at 21 hours	Group R (n = 26)	Group RF (n = 26)	p value*
Excellent	8 (30.8%)	10 (38.5%)	0.504
Good	15 (57.7%)	14 (53.8%)	
Fair	3 (11.5%)	2 (7.7%)	

* χ^2- test for trend

CHAPTER 5

DISCUSSION

The primary goal of postoperative epidural analgesia with local anesthetic agents includes improved analgesia, reduced requirement for supplemental opioids and minimum motor blockade to permit early ambulation, accompanied by an acceptable incidence of side effects.

Though effective analgesia was achieved, this study could not show the benefit of reducing concentration of ropivacaine from 0.2% to 0.1% in order to decrease the incidence of motor blockade. Based on the lower boundary of 95% CI, no significant difference was detected at 4 and 8 hours of infusion. One possible explanation might be the difference in the population is not as much as expected, so the sample size used in this study did not have enough power to demonstrate such difference. However the difference in rate of motor blockade increased over time, this implied the benefit of low concentration of ropivacaine on motor blockade. Significant difference in motor blockade was demonstrated at 21 hours. At that time, after abdominal hysterectomy, the patients should be able to start ambulation such as standing or walking around their bed. Weakness from motor blockade inhibits ambulation from instability while walking. It also makes the patients feel uncomfortable. So that one patient in group R withdrew because of this reason.

The difference in rate of motor blockade was also calculated for those who withdrew before completing the follow up. Assuming in the worst scenario; i.e. the patient in group RF got motor blockade while the patient in group R did not. The difference (95% CI) of rate of motor blockade would be 22.2% (-2.8%, 47.3%) which could change the result of the comparison at 21 hours. However, as lower boundary of 95%CI approached zero that is considered to be non clinical meaningful, this favored the protective effect of 0.1% ropivacaine on motor blockade.

Compared with previous studies, the rates of motor blockade in this study were quite high (50%-78% in group R and 23%-67% in group RF) as shown in table 4. This was in contrast with the study by Zaric *et al.* (31), all subjects who received 0.1%

ropivacaine 10 ml/hr via L_{2-3} catheter had no motor blockade at 4, 8 and 21 hours. In those who received 0.2% ropivacaine, 50% had motor blockade at 4 and 8 hour while 28% had motor blockade at 21 hours of infusion. The possible explanations for the different results are : 1) high concentration of bolus dose used and 2) difference in age and height of the subjects enrolled. The concentration of bolus dose used in Zaric's study was the same as for infusion (0.1% or 0.2% ropivacaine) while this study used 0.75% ropivacaine. There were evidences that intensity and duration of motor blockade increase with dose (46) so the different rate of motor block found in this study can be explained. Etches *et al.* (18) and Jayr *et al*.(16), using 0.5% ropivacaine for bolus dose, reported rate of motor blockade, when assessed at the same period , slightly lower than that found in this study (~30-60%).

The different age and height of the subjects may contribute to the different finding in rate of motor blockade. In Zaric's study, all volunteers participated in the study were healthy men with a mean age of 27 years and mean height of 185 cm. But in this study, the subjects were female with a mean age of 45 years and mean height of 155 cm. The age and height of the patients are considered to be the factors affecting epidural blockade (19). Epidural segmental dose requirement (ERDR) which is the amount of local anesthetics required to block one segment, decreased with age (47). So the rate of motor blockade in this study, even though receiving infusion rate of only 8 ml/hr, were quite high when compared with Zaric's report.

When compare the rate of motor blockade with previous study in similar age group, the rate of motor blockade may also depend on the site of catheter. Motor blockade with 0.2%ropivacaine reported by Jorgensen *et al.* was only 7% with catheter insertion at T_{10-11} (14). The low incidence is most likely due to the use of thoracic catheter. With lumbar catheter, Jayr *et al*., using L_{1-2} level, reported 35-50% motor blockade with 0.2% ropivacaine infusion at 10 ml/hr (16) while Etches *et al*., though using T_9-L_4 but mostly T_{12}- L_3, reported 30-60% motor blockade with 0.2% ropivacaine infusion at 8 ml/hr (18). In this study most patients received epidural catheter insertion at L_{2-3} level, which may also contribute to the high rate of motor blockade.

However when compare with Chinachoti *et al*., using the same level of catheter insertion (17), the rate of motor blockade in 0.2% ropivacaine group found in this study

was also higher (63% VS 55% and 50% VS 20% at 8 and 21 hours respectively). The difference could be due to the different pattern of infusion. This study used constant rate of infusion while the rate in Chinachoti 's study, though started at 8 ml/hr, could be reduced if there were evidences of excessive block until regression. So the rate found might be the results of infusion rate which was less than 8 ml/hour. Moreover some patients in this study (3 in group R and 8 in group RF) received additional dose of 0.75% ropivacaine during surgery which might contribute to the higher rate of motor blockade. Tuttle *et al*. reported the duration of lower extremities block, produced by single injection of 0.75% ropivacaine for lumbar epidural anesthesia, about 310+/-65 minutes (48). Repeated administer of either bolus or continuous infusion of local anesthetic into the lumbar area may increase risk of motor weakness in the lumbar dermatome (37).

Despite the high rate of motor blockade, this study had shown that lumbar epidural analgesia could provide effective pain control after abdominal hysterectomy. The median resting and on coughing VAS pain score were lower than 30 at every measurement in both groups. The addition of fentanyl 2 mcg/ml to 0.1% ropivacaine provided comparable VAS with that yielded by 0.2% ropivacaine alone. This is in accordance with previous study by Scott *et al*., which reported comparable VAS between 0.2% ropivaciane alone and 0.1% ropivacaine plus 2 mcg/ml fentanyl for continuous infusion after major abdominal surgery(49). According to the study by Scott *et al*., only 4 mcg/ml fentanyl in 0.1% ropivacaine yielded significantly lower VAS than 0.2% ropivacaine alone. The possible explanation is that, because of the lipophilic nature of fentanyl, the epidural vasculature and fat absorbed a large proportion of a given dose before reaching the spinal cord. Direct spinal cord effects are only achieved by using fentanyl at 4 mcg/ml. As a result, the opioids related side effects such as pruritus and nausea vomiting will be predictably more common with high dose fentanyl. This is the rationale to use 2 mcg/ml of fentanyl in this study. The incidence of nausea/vomiting and pruritus were not different between groups and from the previous study mentioned (49), but lesser degree of severity of nausea/ vomiting were found. This might result from the different kind of surgery, as major abdominal surgery confers higher risk of nausea/ vomiting than gynecologic surgery.

When compare with Jorgensen *et al.,* who used thoracic epidural catheter for postoperative analgesia after abdominal hysterectomy (14), the resting and on coughing median VAS were comparable in 0.2% ropivacaine alone group when assessed at 4 hours of infusion. This might indicate the efficacy of using lumbar catheter for postoperative epidural analgesia in this kind of surgery. However, the VAS at other assessment cannot be compared due to the different time for data collection.

As with VAS, the amount of morphine consumption in this study was quite low, suggesting that effective analgesia be achieved. Though comparable amount of morphine was used during each measurement, there was a trend towards lower morphine consumption as time passed in group RF. Cumulative morphine consumption in group RF was slightly, but significantly, lower than in group R (figure 7). The synergistic effect of opioid and local anesthetic agent in antinociception is believed to be the reason (50).

The upper level of sensory blockade in group RF, which was significantly lower than that of group R at 4 hours of infusion in this study is in accordance with Zaric's report (32). However, the level of sensory blockade after that remained constant and comparable between the two groups as reported by Scott *et al*.(15). The quite constant level of sensory blockade found in this study supports the benefit of stable level of analgesia by using continuous infusion. The median upper level of sensory blockade in both groups could cover the area of incision, again, indicating the efficacy of using continuous lumbar epidural infusion for postoperative analgesia after abdominal hysterectomy.

The high rate of motor blockade from lumbar catheter cannot be diminished by using low concentration of ropivacaine in this study. However this undesirable outcome did not affect patient satisfaction as the two groups rated their satisfaction in comparable degree. Though a patient in group R, who withdrew because of intense motor blockade, was not included in the analysis about satisfaction. Nevertheless this could be an evidence to demonstrate the tendency of unsatisfactory motor blockade produced by 0.2% ropivacaine .

The limitation in this study is that true ambulation was not evaluated. Bromage score may not necessarily reflect the desired outcome of mobilization. This was

emphasized by Brodner *et al.*(51) and Jorgensen *et al.* (14) who found that patients with Bromage score 0 could not ambulate due to other reasons, most often dizziness, and even Bromage grade I weakness precludes ambulation. Any patient with residual motor blockade (Bromage $\geq$ 1) should not be allowed to move from bed. From these reasons, the patients in this study were not asked to test for the ability for ambulation. However, most of the patients could move in or sit on bed during the study period even though they did not try to stand or walk.

CHAPTER 6

CONCLUSION AND RECOMMENDATION

Continuous epidural infusion of local anesthetics using upper lumbar catheter can provide effective postoperative analgesia after abdominal hysterectomy. When compared with 0.2% ropivacaine alone, 0.1% ropivacaine plus fentanyl 2 mcg/ml yielded comparable analgesia in terms of VAS both at rest and on coughing. The rates of motor blockade were not inferior when assessed at 8 hours. After that, it produce less motor blockade. The comparable amount of rescue analgesic was used at 4, 8 and 21 hours but total amount of morphine consumption was lower with 0.1% ropivacaine plus fentanyl. Side effects were found in acceptable degree and high level of patient satisfaction was achieved.

Since lower concentration of local anesthetic confers lower risk of toxicity if intravascular migration of epidural catheter occurred, 0.1% ropivacaine plus fentanyl could be a better alternative in postoperative epidural analgesia.

Further study with larger number of subjects is required to estimate the more precise difference in rate of motor blockade between these two regimens. The appropriate rate of infusion with lumbar catheter in Thai patients should be explored in order to find the effective analgesia with the least motor blockade.

REFERENCES

1. Lubenow T, Ivankovich A, Mccarthy R. Management of acute postoperative pain. In: Barash P, editor. Clinical Anesthesia. 3 rd ed. Philadelphia: Lippincott-Raven Publishers; 1996. p. 1305-37.
2. Breivik H. High- tech versus low- tech approaches to postoperative pain management. In: Devor M, Rowbotham MC, Wiesenfeld- Hallin Z, editors. Proceeding of the 9th world congress on pain, Progress in pain research and management. Seattle: IASP Press; 2000. p. 787-807.
3. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. Anesthesiology 1995;82:1474-1506.
4. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 1987;66:729-36.
5. Ballantyne JC, Carr DB, deFerranti S. The comparative effects of postoperative analgesic therapies on pulmonary outcomes: cumulative meta-analyses of randomized, controlled trials. Anesth Analg 1998;86:598-612.
6. Capdevila X, Barthelet Y, Biboulet P. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitaion after major knee surgery. Anesthesiology 1999;91:8-15.
7. Love W, Rathmell JP, Tarver JM. Regional anesthesia for acute pain management. Problems in anesthesia 2000;12:165-76.
8. Markham A, Faulds D. Ropivacaine. A review of its pharmacology and therapeutic use in regional anaesthesia. Drugs 1996;52:429-49.
9. Brown DL, Carpenter RL, Thompson GE. Comparison of 0.5% ropivacaine and 0.5% bupivacaine for epidural anesthesia in patients undergoing lower-extremity surgery. Anesthesiology 1990;72:633-6.
10. Kerkkamp HEM, Gielen MJM, Edstrom HH. Comparison of 0.75% ropivacaine with epinephrine and 0.75% bupivacaine with epinephrine in lumbar epidural anesthesia. Reg Anesth 1990;15:204-7.
11. Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JA. Comparison of extradural ropivacaine and bupivacaine. Br J Anaesth 1991;66:31-7.

12. Griffin RP, Reynolds F. Extradural anaesthesia for caesarean section: a double-blind comparison of 0.5% ropivacaine with 0.5% bupivacaine. Br J Anaesth 1995;74:512-6.
13. Fischer C, Blanie P, Jaouen E, Vayssiere C, Kaloul I, Coltat JC. Ropivacaine, 0.1%, plus sufentanil, 0.5 microg/ml, versus bupivacaine, 0.1%, plus sufentanil, 0.5 microg/ml, using patient-controlled epidural analgesia for labor: a double-blind comparison. Anesthesiology 2000;92:1588-93.
14. Jorgensen H, Fomsgaard JS, Dirks J, Wetterslev J, Dahl JB. Effect of continuous epidural 0.2% ropivacaine vs 0.2% bupivacaine on postoperative pain, motor block and gastrointestinal function after abdominal hysterectomy. Br J Anaesth 2000;84:144-50.
15. Scott DA, Chamley DM, Mooney PH, Deam RK, Mark AH, Hagglof B. Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery--a dose finding study. Anesth Analg 1995;81:982-6.
16. Jayr C, Beaussier M, Gustafsson U, Leteurnier Y, Nathan N, Plaud B, et al. Continuous epidural infusion of ropivacaine for postoperative analgesia after major abdominal surgery: comparative study with i.v. PCA morphine. Br J Anaesth 1998;81:887-92.
17. Chinachoti T, Niruthisard S, Tontisirin O, Thienthong S, Khunsongkiet P, Payawal F, et al. A double blind randomized study comparing postoperative pain management in Filipino and Thai patients administered ropivacaine epidurally in combination with ketorolac or ketorolac alone following transabdominal hysterectomy. In: Soontranan P, editor. Annual meeting of Royal collage of anesthesiologist of Thailand; 2000 Aug 20; Bangkok: Ruankaew Press; 2000.
18. Etches RC, Writer WD, Ansley D, Nydahl PA, Ong BY, Lui A, et al. Continuous epidural ropivacaine 0.2% for analgesia after lower abdominal surgery. Anesth Analg 1997;84:784-90.
19. Cousins MJ, B.T. V. Epidural neural blockade. In: Cousins MJ, Bridenbaugh PO, editors. Neural blockade in clinical anesthesia and pain management. 3 rd ed. Philadelphia: Lippincott-Raven; 1998. p. 243-321.

20. Liu SS, Allen HW, G.L. O. Patient-controlled epidural analgesia with bupivacaine and fentanyl on hospital wards. Prospective experience with 1,030 surgical patients. Anesthesiology 1998;88:688-95.

21. Kuhn S, Cooke K, Collins M, Jones JM, Mucklow JC. Perceptions of pain relief after surgery. BMJ 1990;300:1687-90.

22. Siddall P, Cousins MJ. Introduction of pain mechanisms: implication for neural blockade. In: Cousins MJ, Bridenbaugh PO, editors. Neural blockade in clinical anesthesia and management of pain. 3 rd ed. Philadelphia: Lippincott-Raven Publishers; 1998. p. 675-99.

23. Jorgensen H, Wetterslev J, Moiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery (Cochrane review).In: The Cochrane Library, Issue 3, 2001. Oxford: update software.

24. McClellan K, Faulds D. Ropivacaine, An update of its use in regional anaesthesia. Drugs 2000;60:1065-93.

25. Arlock P. Actions of three local anaesthetics: lidocaine, bupivacaine and ropivacaine on guinea pig papillary muscle sodium channels (Vmax). Pharmacol Toxicol 1988;63:96-104.

26. Pitkanen M, Feldman HS, Arthur GR, Covino BG. Chronotropic and inotropic effects of ropivacaine, bupivacaine and lidocaine in the spontaneously beating and electrically paced isolated, perfused rabbit heart. Reg Anesth 1992;17:183-92.

27. Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg 1989;69:563-9.

28. Rosenberg P, Heinonen E. Differential sensitivity of A and C nerve fibers to long acting amide local anaesthetics. Br J Anaesth 1983;1983:163-7.

29. Wong K, Chong JL, Lo WK, Sia AT. A comparison of patient-controlled epidural analgesia following gynaecological surgery with and without a background infusion. Anaesthesia 2000;55:212-6.

30. Turner G, Blake D, Buckland M, Chamley D, Dawson P, Goodchild C, et al. Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery. Br J Anaesth 1996;76:606-10.

31. Zaric D, Nydahl PA, Philipson L, Samuelsson L, Heierson A, Axelsson K. The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2%, and 0.3%) and 0.25% bupivacaine on sensory and motor block in volunteers: a double-blind study. Reg Anesth 1996;21:14-25.

32. Zaric D, Nydahl PA, Adel SO, Enbom H, Magnusson M, Philipson L, et al. The effect of continuous epidural infusion of ropivacaine (0.1%, 0.2% and 0.3%) on nerve conduction velocity and postural control in volunteers. Acta Anaesthesiol Scand 1996;40:342-9.

33. Badner NH, Reid D, Sullivan P, Ganapathy S, Crosby ET, McKenna J, et al. Continuous epidural infusion of ropivacaine for the prevention of postoperative pain after major orthopaedic surgery: a dose-finding study. Can J Anaesth 1996;43:17-22.

34. Kampe S, Weigand C, Kaufmann J, Klimek M, Konig DP, Lynch J. Postoperative analgesia with no motor block by continuous epidural infusion of ropivacaine 0.1% and sufentanil after total hip replacement. Anesth Analg 1999;89:395-8.

35. Ericksson-Mjoberg M, Svensson JO, Alumkvist O, Olund A, Gustafsson LL. Extradural morphine gives better pain relief than patient-controlled i.v. morphine after hysterectomy. Br J Anaesth 1997;78:10-6.

36. Russell R, Reynolds F. Epidural infusion of low-dose bupivacaine and opioid in labor. Does reducing motor block increase the spontaneous delivery rate? Anaesthesia 1996;51:266-73.

37. Buggy DJ, Hall NA, Shah J, Brown J, Williams J. Motor block during patient-controlled epidural analgesia with ropivacaine or ropivacaine/fentanyl after intrathecal bupivacaine for caesarean section. Br J Anaesth 2000;85:468-70.

38. Chestnut D, Owen C, Bates J, Ostman L, Choi W, Geiger M. Continuous infusion epidural analgesia during labor: A randomized, double-blind comparison of 0.0625% bupivacaine / 0.0002% fentanyl versus 0.125% bupivacaine. Anesthesiology 1988;68:754-9.

39. Kaneko M, Saito Y, Kirihara Y, Collins JG, Kosaka Y. Synergistic antinociceptive interaction after epidural coadministration of morphine and lidocaine in rats. Anesthesiology 1994;80:137-50.

40. Scott DA, Beilby DSN, McClymont C. Postoperative analgesia using epidural infusions of fentanyl with bupivacaine. A prospective analysis of 1,014 patients. Anesthesiology 1995;83:727-37.

41. Liu SS, Moore JM, Luo AM, Trautman WJ, Carpenter RL. Comparison of three solutions of ropivacaine/fentanyl for postoperative patient-controlled epidural analgesia. Anesthesiology 1999;90:727-33.

42. Campbell MJ, S.A. J, Altman DG. Estimating sample sizes for binary, ordered cathegorical, and continuous outcomes in two comparisons. BMJ 1995;311:1145-8.

43. Armitage P, Berry G, Matthews JNS. Statistical methods in medical research. 4 th ed. Oxford: Blackwell Scientific Publication; 2002.p.613.

44. StataCorp. Stata Statistical Software: Release 6.0. College Station, TX: Stata Corporation. In.; 1999.

45. Diggle PJ, Liang K, Zeger SL. Analysis of longitudinal data. New York: Clarendon Press Oxford; 1995.p.146-68.

46. Zaric D, Axelsson K, Nydahl PA, Philipson L, Larsson P, Jansson JR. Seneory and motor blockade during epidural analgesia with 1%, 0.75% and 0.5% ropivacaine - A double blind study. Anesth Analg 1991;72:509-15.

47. Bromage PR. Aging and epidural dose requirements. Segmental spread and predicability of epidural analgesia in youth and extreme age. Br J Anaesth 1969;41:1016-22.

48. Tuttle AA, Katz JA, Bridenbaugh PO, Quinlan R, Knarr D. A double-blind comparison of the abdominal wall relaxation produed by epidural 0.75% ropivacaine and 0.75% bupivacaine in gynecologic surgery. Reg Anesth 1995;20:515-20.

49. Scott DA, Blake D, Buckland M, Etches R, Halliwell R, Marsland C, et al. A comparison of epidural ropivacaine infusion alone and in combination with 1, 2, and 4 microg/mL fentanyl for seventy-two hours of postoperative analgesia after major abdominal surgery. Anesth Analg 1999;88:857-64.

50. Akerman B, Arwestrom E, Post C. local anesthetics potentiate spinal morphine antinociception. Anesth Analg 1988;67:943-8.

51. Brodner G, Mertes N, Van Aken H, Pogatzki E, Buerkle H, Marcus MA, et al. Epidural analgesia with local anesthetics after abdominal surgery: earlier motor recovery with 0.2% ropivacaine than 0.175% bupivacaine. Anesth Analg 1999;88:128-33.

APPENDICES

Appendix A

ASA physical status classification

ASA I	A normal healthy patient
ASA II	A patient with a mild systemic disease (mild diabetes, controlled hypertension, chronic bronchitis, morbid obesity)
ASA III	A patient with a severe systemic disease that limits activity (angina, obstructive pulmonary disease, prior myocardial infarction)
ASA IV	A patient with an incapacitating disease, life threatening (heart failure, renal failure)
ASA V	A moribund patient not expected to survive 24 hours (ruptured aneurysm, head trauma with increase intracranial pressure)

For emergency operation, add the letter E before classification

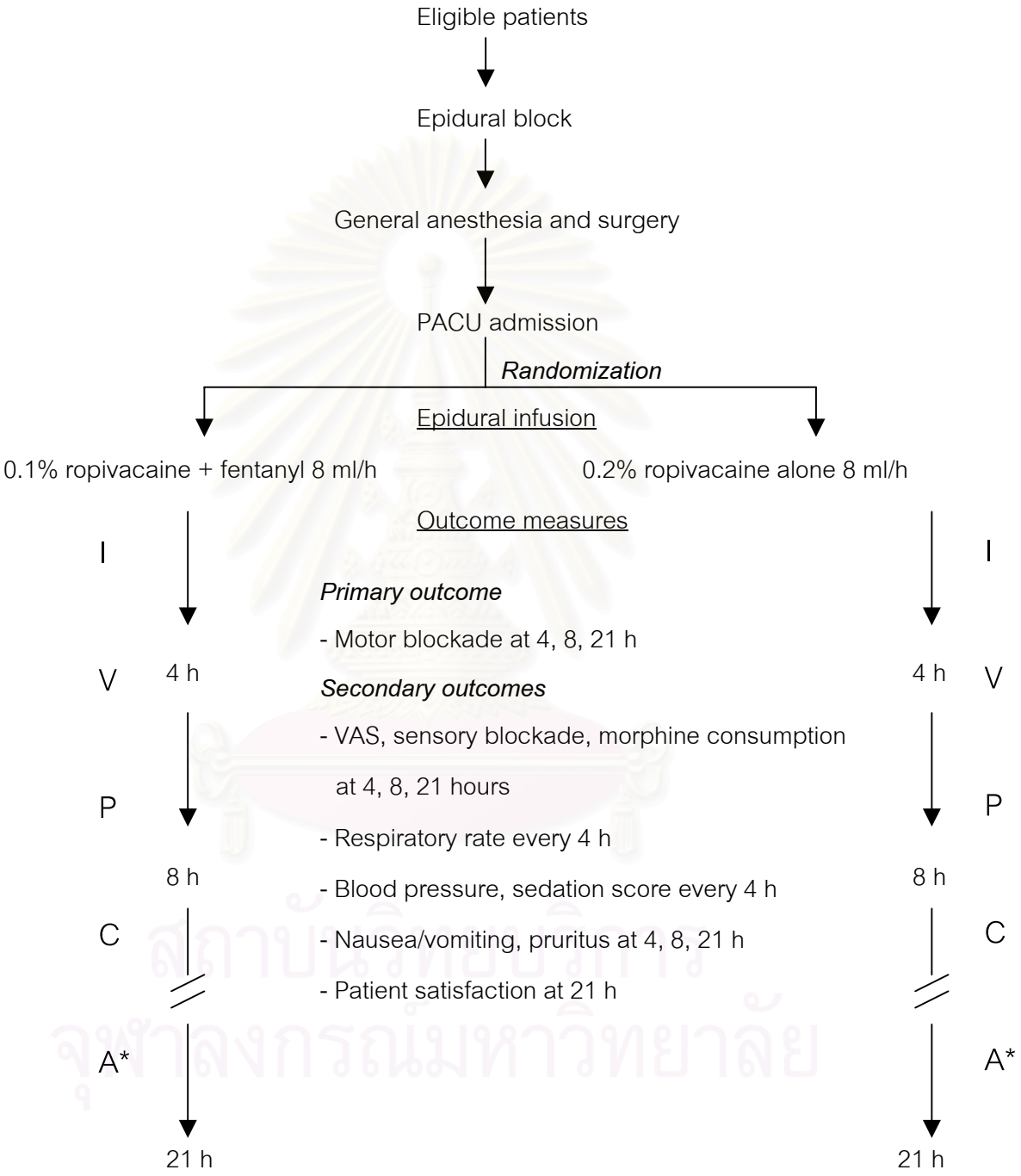
Appendix B

Detail of Drugs Used in General Anesthesia

Premedication	- Midazolam 0.05 mg/kg IV
	- Fentanyl 1 mcg/kg IV
Induction	- Sodium thiopentone 5 mg/kg IV
Intubation	- Succinylcholine 1.5 mg/kg IV
Maintenance	- Nitrous oxide 66% in Oxygen
	- Isoflurane upto 1%
	- Vecuronium 0.08 mg/kg IV and 0.02 mg/kg every 30 minute
Reversal agent	- Atropine 0.02 mg/kg IV
	- Prostigmine 0.05 mg/kg IV

Appendix C

Overview of the Study Design



*IVPCA morphine: 1 mg bolus, 5 min lockout, 4 h limit 20 mg

Appendix D

Consent form

I have been informed that the Department of Anesthesiology, Faculty of Medicine, Khon Kaen University is conducting a study of postoperative pain management in patients undergoing total abdominal hysterectomy by using epidural analgesia. The purpose of this study is to compare the effects of anesthetic drugs such as motor blockade, pain relief, adverse effects and patient satisfaction.

I,_____(the patient's name), agree to participate in this study and understand that it involves:

1. Patients will receive epidural block before surgery.
2. After surgery, the patients will get epidural infusion with either 0.2% ropivacaine or 0.1% ropivacaine plus 2 mcg/ml. fentanyl for 21 hour according to the randomization code together with intravenous patient-controlled analgesia(IVPCA) using morphine.
3. During epidural infusion, research assistant unaware of the drug used assessed the patients about motor blockade, pain score, adverse effects and satisfaction as protocol.
4. In case of inadequate analgesia, the patients can get rescue analgesic by IVPCA. For any possible adverse effects, patients can get rescue drugs whenever require.
5. All information will be kept confidential. No one will be identified individually in any published report. Only the researcher will have access to the data of the study.

I understand that my agreement of participation in this study is entirely voluntary and that I may withdraw my consent to participate at any time without penalty and without anyway affecting the healthcare I receive.

I have opportunity to ask questions about the study and if I have further questions about this study, I may contact the researcher in this hospital on phone number 043-348390.

Research participant's signature _____

Physician's name_____

Witness's name _____

Date of participation_____

ใบยินยอมเข้าร่วมโครงการวิจัย

ข้าพเจ้า(นาง/นางสาว)……นามสกุล……อายุ……ปีอยู่บ้านเลขที่…… ถนน……ตำบล/แขวง……อำเภอ……จังหวัด……โทรศัพท์……

ได้รับฟังคำอธิบายจาก……เกี่ยวกับการเป็นอาสาสมัครในโครงการวิจัยเรื่อง " การศึกษาอาการกล้ามเนื้ออ่อนแรง ที่เกิดร่วมกับการระงับปวด ด้วยวิธีหยดยาชาเข้าช่องเอปิดูราล เปรียบเทียบระหว่าง 0.1 เปอร์เซนต์โรปิวาเคนผสมกับเฟนตานิล และ 0.2 เปอร์เซนต์โรปิวาเคนอย่างเดียวในผู้ป่วยหลังผ่าตัดมดลูกออกทางหน้าท้อง" ว่ามีขั้นตอนอย่างไรบ้าง และได้ทราบ ถึงผลข้างเคียงอันอาจเกิดขึ้น ข้อดี ข้อเสีย เท่าที่ได้มีการศึกษาทดลองแล้ว

ข้าพเจ้าเข้าร่วมโครงการวิจัยนี้ด้วยความสมัครใจ และมีสิทธิที่จะบอกเลิกการเข้าร่วมในโครงการวิจัยนี้เมื่อใดก็ได้ และการบอกเลิกการเข้าร่วมโครงการวิจัยนี้ จะไม่มีผลต่อการรักษาโรคที่ข้าพเจ้าจะพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะดำเนินการด้วยความระมัดระวังอย่างดีที่สุด จะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับ และใช้ข้อมูลที่ได้เพื่อเป็นประโยชน์ในทางการแพทย์ การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆที่เกี่ยวข้องกระทำได้เฉพาะกรณีที่จำเป็นด้วยเหตุผลทางวิชาการเท่านั้น

ผู้วิจัยรับรองว่าหากเกิดความเสียหายจากผลข้างเคียงของการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการรักษาพยาบาลจนปลอดภัยโดยไม่คิดมูลค่า ท่านจะไม่ได้รับเงินการชดเชย แต่แพทย์จะให้คำอธิบายเกี่ยวกับวิธีการตลอดจนยาที่จะได้รับในการรักษาพยาบาลข้าพเจ้า

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้ว และมีความเข้าใจดีทุกประการ และได้ลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ลงนาม……ผู้ยินยอม
(……)

ลงนาม……พยาน
(……)

ลงนาม……ผู้ทำการวิจัย
(……)

……/……/……

Appendix D

Subject Information Sheet

คำชี้แจงผู้ป่วยสำหรับการเข้าร่วมโครงการวิจัย

ชื่อโครงการวิจัย

การศึกษาอาการกล้ามเนื้ออ่อนแรง ที่เกิดร่วมกับการระงับปวดด้วยวิธีหยดยาชาเข้าช่องเอปิดูราล เปรียบเทียบระหว่าง 0.1 เปอร์เซนต์โรปิวาเคนผสมกับเฟนตานิลและ 0.2 เปอร์เซนต์โรปิวาเคนอย่างเดียว ในผู้ป่วยหลังผ่าตัดมดลูกออกทางหน้าท้อง

สถานที่ทำการวิจัย โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

ชื่อแพทย์ผู้วิจัย ผศ. พญ.วิมลรัตน์ กฤษณะประกรกิจ ใบประกอบวิชาชีพเวชกรรม เลขที่ 15760

หลักการและเหตุผล

วิธีระงับปวดที่มีประสิทธิภาพ สามารถใช้บรรเทาความเจ็บปวดที่ไม่อาจหลีกเลี่ยงได้หลังการผ่าตัดใหญ่ ซึ่งนอกจากจะทำให้ผู้ป่วยรู้สึกสบายขึ้นแล้ว ยังทำให้การฟื้นตัวของระบบต่างๆในร่างกายเป็นไปได้รวดเร็ว ลดโอกาสเกิดภาวะแทรกซ้อนทางระบบหายใจ ทางหัวใจและระบบไหลเวียนโลหิตได้ด้วย การให้ยาชาทางช่องเอปิดูราลเป็นวิธีระงับปวดที่มีหลักฐานทางการแพทย์พิสูจน์แล้วว่าได้ผลในดีถึงดีมากหลังการผ่าตัดหลายชนิด ถ้าทำโดยผู้ที่ชำนาญจะมีความปลอดภัยสูง โอกาสเกิดภาวะแทรกซ้อนเช่น ติดเชื้อ เป็นอันตรายต่อระบบประสาทมีน้อย แต่การให้ยาชาอาจทำให้มีอาการหนักขา ขยับส่วนล่างของร่างกายได้ลำบาก เป็นอุปสรรคต่อการเคลื่อนไหวร่างกายซึ่งเป็นสิ่งจำเป็นในการช่วยฟื้นฟูการทำงานของระบบต่างๆและลดการเกิดภาวะแทรกซ้อนดังที่ได้กล่าวมาแล้ว การเลือกใช้ยาชาในขนาดพอเหมาะจะช่วยลดอาการหนักขาลงได้

โรปิวาเคนเป็นยาชาเฉพาะที่ตัวใหม่ที่นอกจากจะมีประสิทธิภาพในการระงับปวดดีพอใช้แล้ว ยังก่อให้เกิดอาการกล้ามเนื้ออ่อนแรงน้อยกว่ายาที่เคยใช้ในอดีต แต่การใช้ยาโรปิวาเคนในคนไทยด้วยขนาดที่แนะนำพบว่าผู้ป่วยจำนวนหนึ่งมีอาการหนักขา ขยับร่างกายไม่สะดวก คณะผู้วิจัยจึงต้องการศึกษาเพื่อหาขนาดยาโรปิวาเคนสำหรับใช้ระงับปวดหลังผ่าตัดที่เหมาะสมกับคนไทย

ข้อมูลของโครงการวิจัย

การวิจัยครั้งนี้เป็นการศึกษาเปรียบเทียบอาการอ่อนแรงของกล้ามเนื้อ ที่เกิดร่วมกับการระงับปวดหลังผ่าตัดมดลูกทางหน้าท้อง โดยวิธีหยดยาชาอย่างต่อเนื่องเข้าช่องเอปิดูราล เปรียบเทียบระหว่างยาโรปิวาเคนสองขนาด คือขนาดที่แนะนำกับขนาดที่ลดลง โดยใช้กลุ่มตัวอย่างเป็นผู้ป่วยที่ยินยอมเข้าร่วมโครงการวิจัยประมาณ 60 คน ผู้ป่วยจะได้รับการให้ยาชาทางช่องเอปิดูราลร่วมกับการวางยาสลบระหว่างผ่าตัดด้วยวิธีมาตรฐานที่ใช้กันอยู่ในปัจจุบัน หลังผ่าตัดผู้ป่วยจะถูกสุ่มเข้ารับยาชาในขนาดใดขนาดหนึ่งเป็นเวลา 21 ชั่วโมง การวัดผลการวิจัยทำโดยเปรียบเทียบผลการตรวจร่างกายและการสัมภาษณ์ระหว่างการให้ยาระงับปวด

ประโยชน์ที่จะเกิดจากการวิจัย

ข้อมูลที่ได้จากการวิจัยนี้จะนำไปสู่การเลือกใช้ขนาดยาที่เหมาะสมแก่ผู้ป่วยหลังการผ่าตัด

<u>รายละเอียดที่จะปฏิบัติต่อผู้สมัคร</u>

ผู้เข้าร่วมโครงการวิจัยทุกคนจะได้รับให้การระงับความรู้สึกระหว่างผ่าตัดด้วยวิธีฉีดยาชาเข้าช่องเอปิดูราลร่วมกับการวางยาสลบ หลังผ่าตัดจะได้รับการสุ่มให้ได้รับยาชาชนิดใดชนิดหนึ่งทางช่องเอปิดูราล ผู้ที่อยู่ในกลุ่มควบคุมจะได้รับยา 0.2 เปอร์เซนต์โรปิวาเคนอย่างเดียว ส่วนผู้ที่อยู่ในกลุ่มศึกษาจะได้รับยา 0.1 เปอร์เซนต์โรปิวาเคนผสมกับเฟนตานิล โดยทั้งสองกลุ่มจะได้ยาหยดอย่างต่อเนื่องเป็นเวลา 21 ชั่วโมงหลังผ่าตัด ระหว่างนั้นทุกรายจะได้ยามอร์ฟีนเป็นยาระงับปวดเสริมทางหลอดเลือดดำด้วยเครื่องมือชนิดผู้ป่วยควบคุมการปวดด้วยตนเอง มีการวัดผลเมื่อเวลา 4, 8 และ 21 ชั่วโมงหลังจากเริ่มให้ยา โดยการตรวจร่างกายและสัมภาษณ์

<u>ประโยชน์ที่จะเกิดแก่ผู้สมัคร</u>

สิ่งที่ผู้เข้าร่วมโครงการวิจัยจะได้รับ นอกเหนือจากการรักษาด้วยวิธีมาตรฐานคือการระงับปวดหลังผ่าตัดด้วยวิธีที่มีหลักฐานพิสูจน์แล้วว่ามีประสิทธิภาพดี โดยไม่เสียค่าใช้จ่ายเพิ่มจากการรักษาตามปกติ

<u>ผลข้างเคียงและความไม่สะดวกที่อาจเกิดจากการทำวิจัย</u>

เนื่องจากยาแก้ปวดที่ใช้ร่วมในการวิจัยนี้ อาจทำให้ผู้ป่วยมีอาการไม่พึงประสงค์บางอย่าง เช่น คันตามร่างกาย คลื่นไส้อาเจียน ง่วงซึม และการหายใจช้าลงได้ อาการเหล่านี้เป็นผลข้างเคียงที่พบได้เมื่อได้รับยาในขนาดสูง อย่างไรก็ตามแม้ในการศึกษานี้จะใช้ยาดังกล่าวในขนาดน้อย ผู้ป่วยทุกรายก็จะได้รับการเฝ้าระวังอย่างใกล้ชิด และหากมีอาการจะได้รับการรักษาโดยไม่เสียค่าใช่จ่ายเพิ่ม

นอกจากนี้ผู้ป่วยจะถูกขอร้องไม่ให้รับยาแก้ปวดอื่นนอกเหนือจากที่กำหนดไว้ และนอกจากการดูแลรักษาตามปกติแล้ว ผู้ป่วยจะได้รับการตรวจร่างกายและสัมภาษณ์ที่เวลา 4, 8 และ 21 ชั่วโมงหลังผ่าตัด ทั้งนี้จะยกเว้นในช่วง 22.00 - 06.00 น.

<u>ท่านจำเป็นต้องเข้าร่วมในการศึกษาวิจัยนี้หรือไม่</u>

การเข้าร่วมในการศึกษาวิจัยเป็นไปโดยความสมัครใจ แพทย์มีหน้าที่ต้องให้การดูแลรักษาผู้ป่วยอย่างดีที่สุด ไม่ว่าท่านจะตัดสินใจเข้าร่วมโครงการหรือไม่ อย่างไรก็ตามแม้ตัดสินใจเข้าร่วมโครงการวิจัยแล้ว ท่านก็สามารถยกเลิกเมื่อใดก็ได้ โดยที่การตัดสินใจดังกล่าวไม่ทำให้ท่านเสียสิทธิในการรับการรักษาพยาบาลที่ถูกต้องตามมาตรฐานแต่อย่างใด

<u>แพทย์ที่ท่านสามารถติดต่อได้</u>

ท่านสามารถสอบถามรายละเอียดเพิ่มเติมได้จาก ผศ.พญ.วิมลรัตน์ กฤษณะประกรกิจ ภาควิชาวิสัญญีวิทยา หมายเลขโทรศัพท์ 3059-60, 348390

Appendix E

Data Collection Form

Trial: Motor Blockade Associated with Postoperative Analgesia: A Comparison between 0.1% Ropivacaine Plus Fentanyl and 0.2% Ropivacaine Alone for Continuous Epidural Infusion after Abdominal Hysterectomy

Principal investigator: Wimonrat Krisanaprakornkit

1. ID number [ ][ ]

Patient's name……Hospital number……Ward…..……...

Address……

Preoperative data

2. Age……yr [ ][ ]

3. Body weight……kg, Height……..cm. [ ][ ] , [ ][ ][ ]

4. ASA status ❑ I ❑ II [ ]

5. Baseline Blood pressure ……/……mmHg

Intraoperative data

6. Level of epidural catheter insertion [ ]

❑ L 1-2 ❑ L2-3

7. Epidural injection of 10 mL 0.75% ropivacine at …… : ……..

8. Additional 5 mL of main dose to achieve T 10 anesthesia [ ]

❑ no ❑ yes at …… : ……..

9. General anesthesia Start at …….. : …….. End at …….. : …….

10. Surgery Start at …….. : …….. End at …….. : …….

11. Additional 5 mL of 0.75% ropivacine during operation [ ]

❑ no ❑ yes at …… : ……..

12. Duration of surgery……minutes [ ][ ][ ]

Postoperative data

13. Epidural infusion Start at …….. : …… End at …….. : …….

14. Reason for stop infusion [ ]

- ❑ As protocol
- ❑ Others……

14. Motor blockade evaluation : using Modified Bromage score

14.1 At 4 hr of infusion, Time: …….. : …….. Bromage score (4) …… [ ]

14.2 At 8 hr of infusion, Time: …….. : …….. Bromage score (8) …… [ ]

14.3 At 21 hr of infusion,Time: …….. : …….. Bromage score (21)…… [ ]

15. VAS score at rest

15.1 At 4 hr of infusion, Time: …….. : …….. VAS score (4 r) ……. [ ][ ] [ ]

15.2 At 8 hr of infusion, Time: …….. : …….. VAS score (8 r) ……. [ ][ ] [ ]

15.3 At 21 hr of infusion, Time:…….. : …….. VAS score (21 r) ……. [ ][ ] [ ]

16. VAS score on coughing

16.1 At 4 hr of infusion, Time: …….. : …….. VAS score (4 c) ……. [ ][ ][ ]

16.2 At 8 hr of infusion, Time: …….. : …….. VAS score (8 c) ……. [ ][ ][ ]

16.3 At 21 hr of infusion,Time: …….. : …….. VAS score (21 c) ……. [ ][ ][ ]

17. IVPCA morphine consumption (from PCA equipment recorded)

17.1 At 4 hr of infusion, Time:…….. : …….. Morphine (4) ……. [ ][ ][ ]

17.2 At 8 hr of infusion, Time:…….. : …….. Morphine (8) ……. [ ][ ][ ]

17.3 At 21 hr of infusion,Time: …….. : …….. Morphine (21) ……. [ ][ ][ ]

17.4 Total morphine consumption Morphine (total) ……. [ ][ ][ ]

18. Level of sensory blockade

18.1 At 4 hr of infusion, Time:…….. : ……..

Upper level (U 4) …….. [ ][ ][ ]

Lower level (L 4) …….. [ ][ ][ ]

18.2 At 8 hr of infusion, Time: …….. : ……..

Upper level (U 8) …….. [ ][ ][ ]

Lower level (L 8) …….. [ ][ ][ ]

18.3 At 21 hr of infusion, Time:…….. : ……..

Upper level (U 21)…….. [ ][ ][ ]

Lower level (L 21)…….. [ ][ ][ ]

19. Blood pressure measurement

19.1 At 4 hr of infusion, Time:…….. : …….. , ……/……mmHg

19.2 At 8 hr of infusion, Time:…….. : …….. , ……/……mmHg

19.3 At 12hr of infusion, Time:…….. : …….. , ……/……mmHg

19.4 At 16hr of infusion, Time:…….. : …….. , ……/……mmHg

19.5 At 20hr of infusion, Time:…….. : …….. , ……/……mmHg

19.6 At 24hr of infusion, Time:…….. : …….. , ……/……..mmHg

20. Hypotension ❑ Yes ❑ No [ ]

21. Respiratory rate

21.1 At 4 hr of infusion, Time:…….. : …….. , RR ……/minute

21.2 At 8 hr of infusion, Time:…….. : …….. , RR ……/minute

21.3 At 12 hr of infusion, Time:…….. : …….. , RR ……/minute

21.4 At 16 hr of infusion, Time:…….. : …….. , RR ……/minute

21.5 At 20 hr of infusion, Time:…….. : …….. , RR ……/minute

21.6 At 24 hr of infusion, Time:…….. : …….. , RR ……/minute

22. Respiratory depression ❑ Yes ❑ No [ ]

23. Sedation score

23.1 At 4 hr of infusion, Time:…….. : …….. , Score……

23.2 At 8 hr of infusion, Time:…….. : …….. , Score……

23.3 At 12hr of infusion, Time:…….. : …….. , Score……

23.4 At 16hr of infusion, Time:…….. : …….. , Score……

23.5 At 20hr of infusion, Time:…….. : …….. , Score……

23.6 At 24hr of infusion, Time:…….. : …….. , Score……

24. Excessive sedation ❑ Yes ❑ No [ ]

25. Pruritus score

25.1 At 4 hr of infusion, Time:…….. : …….. , Score……

25.2 At 8 hr of infusion, Time:…….. : …….. , Score……

25.3 At 21hr of infusion, Time:…….. : …….. , Score……

26. Severity of pruritus [ ]

27. Nausea/ vomiting score

27.1 At 4 hr of infusion, Time:…….. : …….. , Score……

27.2 At 8 hr of infusion, Time:…….. : …….. , Score……

27.3 At 21hr of infusion, Time:…….. : …….. , Score……

28. Severity of nausea/ vomiting [ ]

29. Patient satisfaction ❑ Excellent ❑ Good ❑ Fair ❑ Poor [ ]

Note:……

……

……

Signature :

……Date……..

VITAE

PERSONAL INFORMATION

NAME:	Wimonrat Krisanaprakornkit
DATE OF BIRTH:	August 15, 1965
PLACE OF BIRTH:	Mahasarakham, Thailand
CITIZENSHIP:	Thai
MARRITAL STATUS:	Married

EDUCATIONS

1983-1989	Khon Kaen University, Faculty of Medicine, Khon Kaen, Thailand.
1990-1992	Mahidol University, Faculty of Medicine, Siriraj Hospital, Department of Anesthesiology, Bangkok, Thailand.

CERTIFICATIONS

1989	Doctor of Medicine, M.D. (Hon)
1992	Diplomat of Thai Board in Anesthesiology

PROFESSIONAL BACKGROUND

1990-1992	Residency in Anesthesiology; Siriraj Hospital, Faculty of Medicine, Mahidol University, Bangkok, Thailand
1992-1997	Anesthesiologist and Lecturer, Department of Anesthesiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
1997- present	Assistant Professor in Anesthesiology, Department of Anesthesiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand